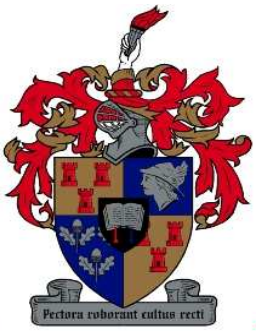

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Mathematical Modelling of the Effectiveness of Two Training Interventions on Infectious Diseases in Uganda

by

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Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and has not previously, in its entirety or in part, been submitted at any university for a degree.

Doreen Ssebuliba Date

Abstract

Nurses, midwives and clinical officers referred to as Mid-level Practioners (MLPs) play an important role in the health care system especially in rural Africa. With particular reference to rural Uganda, due to the large shortage of doctors, MLPs handle most of the duties usually meant for doctors, at health centre IV(s). From 2009 to 2011, two training interventions of MLPs were performed at 36 sites in Uganda by the Integrated Infectious Disease Capacity Building Evaluation (IDCAP). The two interventions were: Integrated Management of Infectious Diseases (IMID) and On-site Support Services (OSS) which aimed at improving MLPs' case management for four diseases: HIV, TB, pneumonia and malaria. In this thesis, we have developed three mathematical models to investigate the effect of the two training interventions on these infectious diseases. All the models are formulated using systems of ordinary differential equations which are structured in three age groups: $[0, 5)$, $[5, 14)$ and $[14, 50)$. We explored the effect of the two training interventions in the context of malaria-pneumonia, HIV-TB co-infections and the four diseases together. Our analysis shows that: i) For malaria-pneumonia, both IMID and the combination of IMID and OSS reduce the number of cases, deaths and prevalence of disease but have no effect on the incident episodes of disease. ii) Results from the HIV-TB model propose that HIV and TB testing are important steps in quality of health care and are capable of offsetting slightly negative effects of reduction in ART enrollment and provision of treatment. iii) The HIV-TB-malaria-pneumonia (HTMP) model concurs with the results of the first two models and its results demonstrate that high coverage levels of the training interventions increase the positive effects that the interventions have on mortality and morbidity. Overall, our results suggest that training of MLPs is much more effective for the short term duration diseases such as malaria and pneumonia, where the baseline values for most of the performance indicators are ≥ 0.6, but not so much for long term duration diseases such as HIV and TB, whose baseline values for most of the performance indicators are < 0.6. The results further highlight that problems such as case detection and drug stock-outs need to be addressed in order for training to have substantial impact, especially in instances where the performance indicator proportions are low.

Opsomming

Verpleegsters, vroedvroue en kliniese beamptes wat gesamentlik na verwys word as mid-vlak praktisyns (MVPs) , speel n belangrike rol in die gesondheidsorg sisteem, veral in landelike dele van Afrika. Met spesifieke verwysing na gesondheid sentrums in Uganda, waar daar te min dokters is, hanteer MVPs die meeste van die pligte wat eintlik deur dokters verrig moet word. Vanaf 2009 tot 2011 is twee opleidingsprogramme vir MVPs by 36 fasiliteite in Uganda deur die Integrated Infectious Disease Capacity Building Evaluation (IDCAP) organisasie aangebied. Die twee programme staan bekend as: Integrated Management of Infectious Diseases (IMID) and On-site Support Services (OSS). Beide die programme stel ten doel om die MVPs se pasint bestuur vir die siektes MIV, tuberkulose (TB), longontsteking en malaria te verbeter. Drie wiskundige modelle word in hierdie tesis ontwikkel om die effek van die opleidingsprogramme op hierdie oordraagbare siektes te ondersoek. Al die modelle word geformuleer deur gebruik te maak van stelsels van gewone differensiaal vergelykings wat gestruktureer is in drie ouderdomsgroepe: $[0, 5)$, $[5, 14)$ en $[14, 50)$. Die effek van die opleidings programme word in die konteks van longontsteking-malaria mede-infeksie, MIV- TB mede-infeksie en al vier siektes gelyk, ondersoek. Die analise wys dat: i) Vir longontsteking-malaria mede-infeksie het beide IMID en die kombinasie van IMID en OSS die aantal siekte-gevalle, sterftes en die prevalensie van die siektes verminder, maar het geen effek op die insidensie van siekte-gevalle nie. ii) Resultate van die MIV-TB model dui aan dat MIV en TB toetsing n belangrike aspek van die gehalte van sorg is en dat dit die effense negatiewe effek van die afname in ART inskrywing en voorsiening van behandeling, teenstaan. iii) Die MIV-TB-longontsteking-malaria model (HTMP) stem ooreen met die resultate van die bogenoemde twee modelle en demonstreer dat ho dekking van die opleidingsprogramme die positiewe effek van die programme op mortaliteit en morbiditeit verhoog. In geheel stel die resultate van hierdie studie voor dat die opleiding van MVPs baie meer effektief is vir die korttermyn siektes soos malaria en longontsteking waarvoor die meeste van die beginwaardes van die prestasie-aanwysers ≥ 0.6 is, maar nie soveel vir lang-termyn siektes soos MIV en TB waarvoor die meeste van die beginwaarde van die prestasie-aanwysers < 0.6 is. Die resultate dui verder aan dat opleiding nie voldoende is wanneer die prestasie-aanwysers < 0.6 is nie en dat probleme soos die opsporing van siekte-gevalle en n gebrek aan medisyne by die klinieke aangespreek moet word vir opleiding om aansienlike impak te he.

Dedication

This thesis is dedicated to my precious daughter, Mary Josephine Nantege. You inspire me.

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List of Abbreviations

ACT	Artemisinin Combination Therapy
AIDS	Acquired Immune Deficiency Syndrome
ARI	Acute Respiratory Infection
ART	Antiretroviral Therapy
CTX	Cotrimoxazole Prophylaxis
DDT	Dichlorodiphenyltrichloroethane
HIV	Human Immunodeficiency Virus
IDCAP	Integrated Infectious Disease Capacity-Building Evaluation
IDI	Infectious Diseases Institute
IMAI	Integrated Management of Adult Illness
IMCI	Integrated Management of Childhood Illness
IMID	Integrated Management of Infectious Diseases
MLPs	Mid-Level Practitioners
MSMs	Men who have Sex with Men
MTB	Mycobacterium Tuberculosis
OSS	On-site Support Services
PCR	Polymerase Chain Reaction

PCV7 7-valent Pneumococcal Conjugate Vaccine

PEPFAR President's Emergency Plan for AIDS Relief

PMTCT Prevention of Mother to Child Transmission

RDTs Rapid Diagnostic Tests

SSA Sub-Saharan Africa

TB Tuberculosis

US United States of America

WHO World Health Organisation

Chapter 1

Introduction

1.1 Background: Infectious diseases

In this world that is faced with disease, the need to develop and strengthen existing health systems is necessary. This has been done mainly through provision of equipment and drugs, capacity building and advances in technology. Moreover, in developing countries such as Uganda, the need to increase manpower and build capacity to handle infectious diseases has been noted.

Infectious diseases are caused by micro-organisms such as bacteria, fungi, viruses or parasites. They are transmitted directly or indirectly from one person to another. Direct transmission may be through contact with droplets from an infected individual by coughing, sneezing, talking, singing, kissing as is the case with TB and pneumonia. Other diseases such as infection with HIV are spread mostly through sexual intercourse. Transmission may also be indirect by involving a vector as is the case with malaria.

1.1.1 Malaria

Malaria is a vector-borne disease that is transmitted by the female anopheles mosquito and caused by a parasite, plasmodium. There are four different species leading to malaria infection and disease among humans. These are: plasmodium falciparum, plasmodium vivax, plasmodium malariae and plasmodium ovale. Plasmodium falciparum is the most

common and life threatening.

In 2009, World Health Organisation (WHO) [201] estimated that the number of malaria cases were 225 million and the number of deaths were 781,000. In 2008, malaria accounted for 8% of all deaths in children less than five years of age globally and 27% of all deaths in children less than five years of age in Africa [201].

Malaria life cycle starts with plasmodium parasites entering the human blood stream in the form of sporozoites that are injected by infected female anopheles mosquitoes while taking a blood meal. After infection, most of the sporozoites migrate to the liver where they invade the liver cells and multiply forming merozoites. The merozoites are released into the blood stream, they attack the red blood cells and lead to the development of the asexual multiplication cycle. A proportion of the merozoites develop into gametocytes which are the transmissible form of the parasite to the mosquito. These are ingested by mosquitoes and go on into the mid gut of the mosquito after developing into oocysts. They are then taken into the salivary glands as sporozoites waiting to be injected into a human and the cycle continues as before.

1.1.2 Pneumonia

Pneumonia is an inflammatory condition of the lung. It affects the alveoli mostly and is associated with fever, rapid respiratory rate, difficulty in breathing, chest in-drawing, abnormal chest sounds and a lack of air space on a chest X-ray. It results from infection by bacteria, viruses, fungi and parasites and these can be acquired outside of health care settings or in a health care setting.

While there are a number of pathogens that cause pneumonia, infection by Streptococcus pneumoniae (*S. pneumoniae*) is the most common cause. The different kinds of pneumonia derive their names from the pathogen of infection or from the setting in which they are acquired.
Thus there is bacterial pneumonia (mostly occurs after bacteraemia -presence of bacteria in blood), viral pneumonia, community-acquired pneumonia, hospital-acquired pneumonia, to mention but a few. Pneumonia is also classified as an Acute Respiratory Infection (ARI).

Globally, it is estimated that over two million children under five die from pneumonia per year [119, 161]. WHO also estimates that up to one million of these deaths are caused by Streptococcus pneumoniae and over 90% of these deaths occur in developing countries.

Pneumonia occurs because of a weakening of the host defences, invasion by virulent organism or invasion by a large inoculum of infectious agent [116].
It mostly follows an upper respiratory tract illness that permits invasion of the lower respiratory tract by bacteria, viruses, or other pathogens that trigger an immune response and produce inflammation [116]. The agents that cause lower respiratory tract infection are most often transmitted by droplet spread resulting from close contact with a source case.

Most bacterial pneumonias are the result of initial colonization of the nasopharynx followed by aspiration or inhalation of organisms [116].
Invasive disease most commonly occurs upon acquisition of a new serotype of the organism with which the patient has not had previous experience, typically after an incubation period of one to three days.

1.1.3 Human Immunodeficiency Virus (HIV)

HIV is the causative agent of AIDS. It targets the immune system of the infected individual and weakens it making the individual incapable of resisting attack from a wide range of infections such as TB, Kaposis Sarcoma, malaria and pneumonia.
Transmission of HIV occurs via exchange of body fluids such as blood, breast milk, semen and vaginal secretions from the infected individual to the uninfected one.
Following infection with HIV, development of AIDS in infected individuals may take 2 to 15 years [202] and it is characterised by development of certain cancers such as Kaposis Sarcoma and other diseases such as active TB.

WHO estimated that there were approximately 34 million people living with HIV in 2011 with Sub-Saharan Africa (SSA) being the most affected region with almost one in every 20 adults living with HIV [202].

Currently, there is no cure for HIV infection but there exists effective treatment with antiretroviral drugs that can control the virus such that individuals can have healthy and

productive lives.
In 2011, WHO estimated that more than 8 million people living with HIV were receiving Antiretroviral Therapy (ART) in low and middle-income countries [202]. By the end of 2011, 54% of the people eligible for treatment were receiving ART.

1.1.4 Tuberculosis (TB)

TB is an airborne infection caused by Mycobacterium Tuberculosis (MTB). It typically attacks the lungs but can also affect other parts of the body. TB infection occurs when droplet nuclei containing tubercle bacilli are inhaled into the lungs and deposited in the alveoli. It is spread when individuals with active TB disease cough, sneeze, laugh or sing.

Most of the infections are latent and about 10% of these latent infections progress to active disease. However, in those with HIV, the risk of developing active TB increases to nearly 10% per year [10, 33].

In 2009, WHO estimated that there were 9.4 million incident cases of TB and 1.3 million deaths due to TB among HIV-negative cases globally [200]. With HIV-TB coinfected individuals considered, there were 1.7 million deaths due to TB globally.

1.2 Control of infectious diseases

Over 9.5 million deaths annually are attributable to infectious diseases and nearly all of them occur in developing countries [196]. In Uganda, over 70% of years of life lost are due to infectious diseases [204].

Control and management of the spread of infectious diseases can be done through various interventions such as case detection and treatment for TB, use of bed-nets, mosquito spraying, use of antimalarials for malaria, use of antibiotics for pneumonia and use of condoms, cotrimoxazole prophylaxis use and ART roll out for HIV.

Though such interventions are in existence, many people, especially in rural Africa, with particular reference to Uganda, lack access to needed preventive and treatment care. This is worsened by the poor and weak health systems characterised by lack of appropriate

infrastructure, insufficiently trained personnel, drug stock outs, to mention but a few [100, 135, 155].
Improvement is needed in all areas of the health system and it is important that human capacity is built to handle the rising demand of health services. Moreover, due to the shortage of doctors, it has been noted that Mid-Level Practitioners (MLPs) are taking on duties that are meant for doctors even though, in some cases they are not well equipped to handle those duties. This calls for training initiatives to facilitate and equip MLPs.

1.3 Training interventions

These have been disease specific for the most part and have evaluated the quality of care through intermediate outcomes such as proportion of patients who are referred for laboratory testing and those who are prescribed appropriate medication [143, 180]. Though there is evidence that shows improvement in case management with disease specific training [143, 180], some studies have shown that it may worsen quality of care for another disease that is not being considered [154, 158].

Moreover, training methods have largely been classroom based with little or no follow-up reinforcement and no supervision, even though existing evidence suggests that knowledge gained through classroom training is not applied when the trainee returns to his/her real world clinical setting [42], and that on-site training and supervision [146, 147] can have a positive effect on clinical practice [155]. In addition, little work has been done on evaluating training methods, and training approaches differ in both course content and delivery.
With the global health community being geared towards training a considerable number of health workers as was evidenced by the President's Emergency Plan For AIDS Relief (PEPFAR)'s reauthorisation bill of 2008, there is a need to know which training approaches yield the best and most lasting results.

It is in this regard that Integrated Infectious Disease Capacity-Building Evaluation (IDCAP) carried out a study at 36 sites in Uganda to evaluate the effectiveness of two training approaches: Integrated Management of Infectious Diseases (IMID) and On-site Support Services (OSS) [62, 122]. It built on the already existing WHO's Integrated Management of Childhood Illness (IMCI) and Integrated Management of Adult Illness (IMAI) training

programs.

1.4 Motivation of project

The shortage of doctors in sub-Saharan Africa (SSA) has led to a shift in handling of health tasks. Duties that were conventionally carried out by doctors are now being handled by MLPs. Moreover, MLPs report that they lack enough training to carry out such activities [112] and other studies have noted that MLPs do not have adequate skills and knowledge for integrated management of diseases [139, 153].

Besides, the effect of training of MLPs has focused on intermediate outcomes on the quality of care [132, 143, 180] and little on final outcomes such as morbidity and mortality. The reason for this being that statistical analysis of data is limited since it only shows the impact of the interventions on the intermediate outcomes, and deals with one disease at a time. Moreover, it is hypothesised that if demonstrated effectiveness of training is maintained and the intervention is expanded to achieve sufficient coverage levels, it could result in considerable impact on population health [155]. It is in this regard that use of a mathematical model is helpful in providing information about the incidence, prevalence and mortality of disease in the population.
A mathematical model provides a framework for synthesizing all available information (demographical, epidemiological and programmatic (IMID and OSS)) and producing quantitative results. It can be used for short term and long term projections of the impact of the interventions being studied and also investigate insightful scenarios. Furthermore, it can be used in an integrated framework of two or more diseases.

It is for this reason that we employ the use of mathematical models in this thesis which will help in quantifying the effects of the two training interventions that were carried out by IDCAP at 36 sites in Uganda. Addressing this gap in knowledge is very important and we are thus motivated to do this work due to the impact it can have on health policy in Uganda and Africa at large.

1.5 Objectives of the study

The main goals of the study are:

1. To review literature on the four infectious diseases of malaria, pneumonia, TB and HIV and on training interventions.
2. To develop mathematical models of malaria-pneumonia co-infection, HIV-TB co-infection and co-infection of the four diseases.
3. To link data on case management of disease to transmission dynamics of the diseases.
4. To investigate whether training interventions have an impact on mortality, prevalence and incidence of disease.

1.6 Description of project

The primary purpose of this research project is to formulate mathematical models that help to quantitatively study the effect of two training interventions on management of infectious diseases. The training interventions (IMID and OSS) were implemented at 36 sites in Uganda. The sites were grouped into 2 Arms, Arm A and Arm B with 18 sites each. Both Arms received IMID and Arm A was given OSS. Data were collected and we fitted our models to these data using an optimization tool built in Matlab. More on the IDCAP project is given in Chapter 3.
We formulated three mathematical models, the third being a combination of the first two.

- ★ The first model deals with malaria and pneumonia coinfection. We use the model to assess the effect of IMID and the combination intervention of IMID and OSS on health outcomes such as morbidity and mortality. We also estimate the incremental impact of OSS and investigate the scenario of only doing triage of severe disease cases.
- ★ The second model considers the coinfection of HIV and TB. It is used to explore the effect of the two training interventions on the management of HIV and TB in terms

of ART enrollment, TB case management and health outcomes such as deaths. We conclude by predicting the effectiveness of IMID and OSS for five more years.

★ Model three is a combination of model one and model two. It is an integrated model that considers all the four diseases together, that is HIV, TB, malaria and pneumonia. It is used to investigate the effect of IMID and IMID+OSS in line with an integrated approach of managing all the four diseases. The effectiveness of the interventions is measured in terms of considering the number of deaths that occur with and without the interventions. We also run numerical simulations to determine the effectiveness of the two interventions with a 25% effect on performance indicators and high coverage levels.

1.7 Project outline

In Chapter 2, we present a literature review on mathematical modelling of infectious diseases, HIV, TB, malaria and pneumonia and also literature on training interventions. Chapter 3 gives the IDCAP data and describes the parameters that were obtained from the IDCAP project. In Chapter 4, we look at the model of malaria and pneumonia coinfection and the effect of IMID and combination of IMID and OSS on malaria and pneumonia case management. Chapter 5 is devoted to the modelling of HIV and TB coinfection and also explores the effect of training on management of TB and HIV cases. We then get an overview of an integrated model of the four infections, HIV, TB, malaria and pneumonia and examination of the effect of training with regards to managing these four diseases in Chapter 6. We conclude in Chapter 7 with some recommendations and ideas for future research.

Chapter 2

Literature Review

2.1 Introduction

In this chapter, we will review some mathematical models of malaria, pneumonia, TB, HIV, HIV-TB coinfection and literature on training interventions on infectious diseases. There is a considerable amount of literature on these diseases and many models have been developed for their transmission dynamics. We focus on models which incorporate interventions and are important for our study.
Most commonly used words in this chapter are: susceptibles (individuals who are not infected), latent (infected but not infectious), asymptomatic (infected, can transmit infection but lack symptoms), infectious (infected and can transmit the infection) and symptomatic (infectious with symptoms).

2.2 Malaria models

In this section, we review mathematical models of malaria that are most relevant to our work. We consider compartmental and deterministic models of ordinary and partial differential equations. Starting from the basic Ross model, we work our way to malaria models which incorporate age structure, immunity and interventions and we discuss how our malaria model relates to the already known and published models.

Basic models

In his early work on malaria, Ross proved the role of certain mosquitoes in the transmission of malaria [8, 160]. He built mathematical models to explain his theory that control of malaria could be done by reducing the number of mosquitoes. He also sought answers to why the disease varied from place to place and even in the same place, from season to season or from year to year [160]. Ross considered two differential equations [8, 115], one for the number of infected humans with malaria and another for the number of infected mosquitoes. His conclusions from this study were that the increase or decrease of malaria depended on a certain threshold in the number of mosquitoes and it was not necessary to eliminate all the mosquitoes in order to eradicate malaria. This model was later modified by Macdonald by considering proportions of infected mosquitoes and humans instead of numbers and is popularly known as the Ross-Macdonald model [115].

Macdonald extended the model by Ross to account for the latency period of the parasite in mosquitoes [96, 115] by introducing the latent class for mosquitoes and this model was later extended by Anderson and May [5] to include a latent class in humans as well. This idea of latency showed that survival of the adult female mosquito was very important in the spread of malaria and this provided the rationale for a campaign by WHO to use insecticide DDT to kill mosquitoes. Furthermore, these models focused on studying the parameters of the mosquitoes such as biting rate, the death rate and the ratio of mosquitoes to humans to explain how spread of malaria could be controlled.

There are other factors such as age and immunity of an individual, climate and environment of an area that influence malaria that were not incorporated in the first four models we reviewed. For the case of age and immunity, malaria infection depends on an individual's age and individuals tend to gain immunity as they grow older. Immunity can be described in a number of responses such as: loss of infectivity, increase in recovery rate, loss of detectability and decrease in susceptibility [46, 59].

Age structure

Anderson and May included age structure in the Ross model by considering the population of humans as a function of time and age [5, 115]. This improved on the basic Ross model but its predictions did not match the data well which made it clear that the interaction

between age and immunity should be modelled explicitly.

Immunity

The model by Dietz et al. [46] used non linear difference equations to define the dynamics of the human population. Immunity was assumed as being in the form that a vector which bites a non-immune host is more infectious than a vector that bites an immune host. Three aspects of immunity were considered, loss of infectivity, increase in recovery and decrease in detectability. The model was fitted to data and there was some agreement between the observed data and the model values.

In [26], Boni et al. used a model that considered the concept of semi-immunity to study the effect of multiple first line therapies in presence of resistance evolution in strains of malaria parasites. The model had three major classes: susceptible class, asymptomatic class and symptomatic class. The concept of immunity was summarised in the way individuals responded to malaria infection and their infectiousness potential. Individuals who were naive easily developed symptoms after infection while semi-immune hosts rarely developed symptoms after infection. Both naive and semi-immune hosts in asymptomatic class progressed to symptomatic disease with naive individuals developing clinical disease more often than semi-immune hosts. Semi-immune hosts were considered to be less infectious than naive hosts.

Age and Immunity

Filipe et al. [59] used a model of a system of partial differential equations of age and time. It examined the development and acquisition of immunity to malaria. In the model, acquired immunity was represented by three immunity functions which are responses to malaria. These were: reducing the likelihood that an infected person develops symptomatic disease, increasing the rate at which infection is cleared and also increasing the duration of low-level infections. The model suggested that immunity to symptomatic disease lasts for at least 5 years, and develops faster if there are higher levels of infection in the population, and increases with age. Immunity to clear infection lasts longer (it can last for 20 years or more), develops later in life, and does not depend on the amount of transmission in the population. On the other hand, the clearance of low-level infections was not important in explaining the epidemiological trends observed.

Okell et al. [151], developed a deterministic age-structured mathematical model with five states: susceptibles, latent, infectious and untreated, infectious and treated, and protected, to study the impact of Artemisinin Combination Therapy (ACT) on malaria transmission intensity. Immunity was modelled by incorporating age-dependency in the probability that an infectious bite develops into a blood stage infection, the proportion of infections which become symptomatic, the rate at which infection progress to the final low-level infection stage and the infectiousness to mosquitoes. Data from a survey in Tanzania was used to characterise rates of infection, symptomatic episodes and use of antimalarials before the introduction of ACT. The results from the model suggested that ACTs have the potential to reduce transmission to levels approaching those achieved by insecticide-treated nets in lower transmission settings.

Seasonality

Bacaër [7] gave an approximate formula involving two terms for the basic reproduction number, R_0 of a vector-borne disease when the vector population has small seasonal fluctuations of a periodic nature. The basic reproduction number R_0 is defined through the spectral radius of a linear integral operator and numerical methods for the computation of R_0 are given.

Dembele et al. [44] studied a malaria model with periodic mosquito birth and death rates. They used periodic coefficients in the system of one-dimensional equations and these accounted for the seasonal variations (wet and dry seasons) in the mosquito birth and death rates. An R_0 is defined for periodic coefficients and it is shown that the disease goes extinct if R_0 is less than unity and it is endemic if it is greater than unity and may even be periodic.

Chitnis et al. [37], developed and analysed a periodically-forced difference equation of model for malaria in mosquitoes that captured the effects of seasonality and allowed the mosquitoes to feed on an heterogeneous population of hosts. Their numerical results showed the existence of a unique globally asymptotically stable periodic orbit and periodic orbits of field-measurable quantities that measure malaria transmission. They also used the model to compare the effects of insecticide-treated nets and indoor residual spraying on malaria transmission, prevalence and incidence and it was found that insecticide-treated nets were more effective in reducing malaria transmission and prevalence than indoor residual spray-

ing but indoor residual spraying takes less time to eradicate malaria. The results showed that the interventions' reduction in malaria transmission is offset with an increase in clinical malaria.

Though our mosquito birth rate is time dependent and accounts for the effects of seasonality, it is not periodic. The articles we have reviewed helped us in understanding the importance of seasonality and how this may be modelled in mathematical models.

Case management

Tediosi et al. [186], developed a dynamic model that incorporated case management of malaria into it. Their argument was that most models of cost-effectiveness of malaria control interventions assume that incidence of illness and transmission of disease are independent of the case management system, yet the management of disease in the health care system has potential impact on malaria transmission and incidence. Their model compares outcomes of different case management regimens in different transmission settings and it considers asymptomatic malaria, symptomatic malaria and severe malaria. Though it differs from our model in that it is a combination of dynamic model of stochastic simulation with decision tree analysis and it was constructed to look at cost-effectiveness, it raises the importance of incorporating transmission dynamics of disease with the health care system.

In summary, the Ross and Ross-Macdonald [8, 115, 160] models motivated our development of a relatively simple model, since their model involved only two equations (for infected humans and infected mosquitoes) with no latent classes, and yet still yielded valuable insight into the control of malaria.
The study of parameters to explain how malaria could be controlled through use of interventions also informed our own work as we considered certain parameters such as the recovery rate to study the effect of training interventions.
Models with concepts of age and immunity [26, 46, 59, 115, 151], and those with seasonality were also important for our study when we were considering how to incorporate these concepts in our models.
Where as Boni et al [26] and Tediosi et al. [186] had a class of asymptomatic individuals, they did not integrate the asymptomatic and susceptibles together as we have done with our models. Moreover, none of the other models we reviewed and that we know of have considered a class of both susceptibles and asymptomatic individuals together.

Lastly, it is important to point out that none of these earlier malaria models studied the effect of training interventions, and our work addresses this gap.

2.3 Models of pneumonia

We review some models of pneumonia, both mathematical and statistical. Our focus is on models that provided estimates of parameters that we used when simulating our models in later chapters. We also deal with models that included interventions such as vaccination and treatment.

Smith et al. [176], used a stochastic model to estimate the acquisition and invasiveness of different serotypes of *S. pneumoniae* by fitting the stochastic model to longitudinal carriage data in children from Papua New Guinea. Frequent invasion was associated with a high acquisition rate and high frequency and prolonged duration of carriage. Parameters of acquisition and invasiveness from this study informed the parameter values in our model.

In [120], Melegaro et al. considered a stochastic model of pneumococcal carriage. It had two groups, children and adults and the states considered were susceptible and infected. Invasiveness of disease and death from disease was not considered. Probabilities of transition from susceptible to infected and vice versa were calculated. Parameters such as clearance, community acquisition rate were estimated from carriage data. It was noted that children had higher pneumococcal carriage prevalence as compared to adults, which was a valuable insight. Results further showed that household acquired transmission made a major contribution to pneumococcal carriage transmission in families.

Temime et al. [187], developed a mathematical model of selection for *S. pneumoniae* resistance to penicillin G in an age structured population. The model considered three age classes, that is, $[0, 2)$ years, $[2, 15)$ years and 15+ years. The model incorporated vaccination and sought to understand the epidemiological characteristics of *S. pneumoniae* in a vaccinated population and also the distribution of resistance levels in children and adult carriers after introduction of vaccination. The results suggested that because of serotype replacement, the effects of vaccination observed at a particular instant would not be sustained in the long run. The insight gained from this model was its use of age structure

and incorporation of vaccination as an intervention.

Huang et al. [80] developed a transmission model to evaluate the risks of attending child-care centres (CCC) and associating with play mates who attend CCCs. The parameters of the model were based on data from a multicommunity study. The model explained the marked differences in carriage across communities. The model was made up of two states, noncolonised and colonised with *S. pneumoniae* in children. This was then extended to include two classes of children, attendees of CCCs and non-attendees. The effect of CCCs on pneumococcal carriage was established in these communities and parameters of transmission, clearance were estimated using the data collected in the communities and these informed some of the parameter values that we used in our model.

Sutton et al. [184] developed a mathematical model for pneumococcal infection with vaccination. It was made up of partial differential equations with time and age as independent variables, though in the analysis these were reduced to differential equations. The model was used to evaluate the impact of vaccines at population level and parameters were estimated using data. Use of vaccination as an intervention, age dependence and estimation of parameters were important aspects that informed our work.

Snedecor et al. [177] developed an age structured transmission dynamic model to quantify the direct and indirect benefits of infant PCV7 vaccination. The model simulated the acquisition of asymptomatic carriage of *S. pneumoniae* and the development of fatal and non-fatal invasive pneumococcal disease. It was parametrised using US data. This model is similar to ours in that it considered asymptomatic carriage of *S. pneumoniae*.

In [51], Effelterre et al. developed a dynamic model of pneumococcal infection to study the implications for prevention of infection through vaccination. The study highlighted that the effects of vaccination on colonisation of *S. pneumoniae* determined the overall benefits in the population.

The models of pneumonia that we have reviewed have aspects of age dependence, colonisation to cause asymptomatic infection, and vaccination as an intervention. These models informed our parameter values and gave us insight in our own model development. However, it is important to note that none of them had a class of symptomatic disease and they did not have an integrated class of susceptibles and asymptomatic individuals. Fur-

thermore, our model also sheds light on the effect of training interventions on pneumonia which is not considered in these reviewed models.

2.4 Malaria-pneumonia coinfection

A number of observational clinical studies have shown evidence of individuals having symptoms of both malaria and pneumonia. Here, we review some studies related to the occurrence of malaria-pneumonia coinfection with particular focus on the proportions of individuals with malaria who have pneumonia, the proportions of those with pneumonia who have malaria, and the effect of malaria-pneumonia coinfection on morbidity and mortality.

Berkley et al. [20] reviewed clinical and laboratory data of Kenyan children whose primary diagnosis was malaria. They wanted to find out what the incidence and clinical importance of bacteraemia (pneumonia) in severe malaria were. The overall incidence of bacteraemia in severe malaria was 7.8% but it was 12.0% in children under 30 months of age. There was a 3-fold increase in mortality with bacteraemia present in children with severe malaria. Their conclusion was that bacteraemia may contribute to the severity of malaria and thus recommended that children with severe malaria should be treated with both antimalarials and antibiotics.

Evans et al. [54] carried out a study where 12% of malaria patients had bacteraemia. Though severe malaria and bacteraemia were not positively associated, patients who where smear positive for malaria and those smear negative for it could not be distinguished on the basis of symptoms alone. The recommendation from this study was that infants with symptoms of severe malaria but smear negative for it should be given antibiotics.

In [99], Källander et al. carried out IMCI at health facilities to determine the extent of overlap of symptoms of malaria and pneumonia. IMCI is presumptive considering fever for malaria and cough and fast breathing for pneumonia. 3671 children under five years of age were evaluated at 14 health centres in Uganda. 30% of these had symptoms for both malaria and pneumonia. Moreover, 37% of 2944 malaria cases also had pneumonia. It is important to note that this study was observational and not laboratory based.

An observational study reported by Berkley et al. [19] used clinical syndromes to decide on

giving children antibiotics. Children under five years of age were considered. $4.0\% - 8.8\%$ of malaria film positive patients had an invasive bacterial infection and it was concluded that having malaria parasitaemia should not lead to withholding of antibiotics.

Bassat et al. [16] carried out a study which found that 5.4% of children with severe malaria also had bacteraemia and case fatality rate rose when bacteraemia was involved. The death rate of individuals with malaria-pneumonia coinfection was higher than that for individuals with one of the diseases. The case fatality of severe malaria cases who also had bacteraemia was 22.0% yet that of severe malaria cases only was 4%.

In this subsection, we have reviewed studies of coinfection of malaria and pneumonia. It is a common occurrence most especially in children less than 5 years of age and it warrants modelling in order to quantify the prevalence of malaria and pneumonia coinfection in a particular setting. Our model address this gap since, to the best of our knowledge, there is no mathematical model that investigates malaria-pneumonia coinfection.

2.5 HIV models

Numerous models for the dynamics of HIV infection and AIDS disease have been developed. Early models concentrated on the transmission dynamics of the disease and recent models have focused on interventions for control of the disease. With the era of ART, some models have incorporated the use of ART and have investigated the potential impact of increase in the numbers of people receiving ART [11, 23, 64]. Others have incorporated age structure and have time dependent parameters [11, 71].

To the best of our knowledge, no mathematical model has explicitly modelled CTX. The only model that we know of is the the cost-effectiveness model by Pitter et al. [157] which used cohort data and developed four screening algorithms to put HIV infected individuals onto CTX. Their results showed that CTX was highly cost-effective in rural Uganda. Though we are not doing a cost-effectiveness study, the model by Pitter et al. [157] has some useful information that we took note of in our study.

Models have suggested that the presence of PMTCT reduces the number of children who get infected at birth and those that get infected through breastfeeding. An extensive model

for paediatric HIV that considered the importance of PMTCT was developed by Leigh Johnson [90]. It used population projections from the ASSA2003 AIDS and Demographic model (a model for the South African HIV epidemic) to give the number of births by HIV positive women. Our model formulation is simpler than this as we consider a constant number of HIV positive births.

Gupte et al. [74] modelled HIV transmission through breastfeeding in presence of an imperfect test using a statistical methodology. We gained some insights such as the fact that, for populations in rural Africa where breastfeeding is the norm and duration of breastfeeding is long, it is important to know the transmission probabilities due to breastfeeding.

An early article by Garnett and Herderson [64] on ART examined the effect of HIV transmission with the introduction of ART, considering the fraction of HIV infected individuals receiving ART. Two mathematical models were used.
The first model dealt with the rate at which susceptibles entered into the sexually active class, and also studied the duration of sexual activity and the time when treatment started after infection. It considered that a proportion of the infected individuals is treated, and assumed that AIDS individuals did not take part in the transmission. It allowed for transmission dynamics and parameters such as partner rate turn over and transmission probability.
The second mathematical model explored heterogeneity in sexual groups and allowed for a difference in CD4+ cell density. Depending on the scenario chosen, ART could reduce the burden of disease or increase it. Similarly we also consider the fraction of HIV infected individuals receiving ART.

A model by Blower et al. [23] investigated the impact of ART among Men who have Sex with Men (MSMs), the emergence of drug resistance and increase in risky behaviour. The transmission model also incorporated a statistical approach that helped to show the high uncertainty of the effects of ART. The fraction of individuals taking ART per year was calculated as the rate at which individuals go onto ART divided by a summation of the rate at which individuals die if not on ART, and the natural death rate, and the rate at which they go onto treatment. We also used a similar formulation to calculate the fraction of individuals taking ART. The difference of this model with ours is that we considered testing of HIV positive individuals which was not done in this model.

Bacaë et al [11], used an age structured model is used to model the HIV epidemic in South Africa. It has a time dependent force of infection and it considers annual testing of individuals for HIV and ART enrollment. Itse results suggested that the high levels of reported condom use would be able to cause a long-term decline of HIV. Similarly, we also used a time dependent force of infection and also considered testing of HIV individuals and used their formulation of ART enrollment.

Of crucial importance is the fact that there is no model that we know of that models the effectiveness of training interventions on HIV and our model is novel in this area. In addition, most of the models did not consider testing of HIV positive individuals and neither did they consider use of CTX. In this regard, our model addresses gaps in regard to these three issues.

2.6 TB models

Most basic models of TB consist of three classes: susceptible, latent and active TB and the complex ones build onto these by adding more classes such as the treated and recovered classes or by differentiating latent individuals into those who progress slowly to TB disease and those that progress very fast [10, 24, 31, 32]. They can also include interventions such as vaccination and TB treatment.

Blower et al. [24] formulated two models beginning with a simple model and then a detailed one. The first model comprised susceptible class, latent class and the infectious class. Susceptible individuals are infected and move directly into active class which is called fast progression or they move into the latent class which is known as slow progression and those from the latent class progress to active class later.
In the more detailed model, two active classes were presented, one infectious and one non-infectious, as well as the recovered class. Active TB individuals recover and move into the recovered class.

Castillo-Chavez and Feng [31] presented a model made up of susceptible class, latent class and active class. There was no progression from active class to latent class and there was recovery from the active class and latent class to the susceptible class. In comparison to

our model, the recovery of TB individuals leads them back to the susceptible class which has the latent class embedded in it.

Vynnycky and Fine [192] developed an age-structured model of TB. It dealt with time since infection and the importance of age in the transmission dynamics of TB. There was also some discussion on exogenous reinfection and its contribution to TB prevalence.

In [205], Williams et al. developed a two states TB model with a TB free state and TB disease state. It is similar to ours in that two classes are used but different in that instead of a TB free class, we have a class containing both latent and fully susceptible individuals. Nevertheless, it is not unusual to use two classes to describe TB dynamics.

We gained useful information from these TB models which we used for our own model formulation. None of these TB models considered the concept of having a class of susceptibles together with latent individuals divided into proportions and we did not find any that we know of. It is important to note that none of these models considered the impact of training interventions.

2.7 HIV-TB coinfection

Oluwaseun et al. [172], presented a model of HIV-TB coinfection and discussed the effect of using different treatment strategies: treating TB only, treating HIV only, by use of antiretrovirals or treating both of the diseases. Their study concluded that, in resource limited countries, treating one of the diseases reduces the number of individuals coinfected with HIV and TB more than if the coinfected individuals are treated.

In [10], Bacaër et al. modelled HIV-TB coinfection in a South African township and used data to estimate certain parameters and to investigate the impact of two TB control measures: increased TB detection and TB treatment as well as HIV interventions such as condom promotion and antiretroviral treatment. The first three mentioned were positively effective and ART was effective depending on how much it reduced the infectiousness of individuals who were HIV-positive. The model also suggested that use of ART greatly reduces the TB notification rate.

Bhunu et al. [21], discussed a model of HIV-TB coinfection. It considered ART for HIV and treatment of all the different forms of TB, latent and active. The model was mathematically analysed without any intervention strategy. From their study, ART reduces the number of individuals progressing to active TB, and the number of active TB individuals whose TB treatment is delayed, progressing to AIDS disease.

Both studies in [10] and [21] concluded that the effect of ART on TB (and on HIV) depends greatly on the reduction in HIV transmission that it results in.

In [86], Roeger et al. formulated a model of HIV-TB coinfection. They determined the basic reproductive number and analysed mathematically the model's behaviour. They noted that the increased progression rate from latent to active TB may have an important part to play in the increase of TB prevalence. The model did not consider ART.

All these HIV-TB mathematical models gave us insight in our own model formulation. It is crucial to note that none of the models that included interventions considered the impact of training and our work addresses this gap in knowledge.

2.8 Models with two time scales

Given the mathematical and numerical challenges faced with models of two time scales (fast and slow dynamics), there is limited literature on them. We review some of the ones we found.

Smith et al. [107] studied a model of Sexually Transmitted Disease (STD) where they considered that the model had two time scales; the fast paring dynamics where single individuals form partnerships and the slow dynamics where population of susceptibles interacts with that infected individuals. A time scale approximation known as the quasi-steady state approximation was used for the fast dynamics.

In [14], a model of malaria and HIV was considered and also the quasi-steady state approximation was used by considering that the malaria dynamics are at a faster time scale than the HIV dynamics. It was noted that it was not necessary to model the vector mosquito population explicitly.

We did not find any models of malaria with TB, pneumonia with TB or HIV and pneumonia in our literature search. However, the few articles that we reviewed on the subject of two time scales gave us useful information.

2.9 Training

Training of MLPs is an important aspect in health care. In a recent study carried out in Uganda [112], a training needs assessment among clinicians was done to identify task shifting that had occurred from doctors to clinical officers, nurses and midwives. The study noted that some of the clinicians who prescribed ART to HIV patients did not have enough overall knowledge about it. It was then concluded that training of MLPs should be incorporated in the health care system if task shifting is to be successful.

Some earlier studies [143, 180] had been carried out to examine the effect of training on the management of malaria.
One study on case management of malaria [180] found that after a team based training, there was an increase in the proportion of malaria suspects referred for blood smears and a decrease in the proportion of patients with negative blood smears prescribed medication.

Another study done in Tanzania [143] also found that there was a decrease in prescription of malarial drugs at health centres where health workers were trained in microscopy based diagnosis.

Both these studies showed that there was some benefit to training of health workers even though they were disease specific and ignored the important effect that a disease can have on other diseases and their management.

Studies that have incorporated integrated management of infectious diseases are IMCI studies that were carried out in in five countries: Uganda, Tanzania, Bangladesh, Peru and Brazil [28, 132, 155]. These focused on evaluating the impact of IMCI on health of children under five years of age.

In the Tanzanian IMCI study [132], it was noted that children under five in IMCI districts received better care than children in districts where IMCI was not implemented. It was

also noted that IMCI was likely to result in gains in child survival and improvement in quality of care if sufficient coverage levels could be achieved and maintained.

The Ugandan IMCI study [155] assessed the effects of scaling up of IMCI on the quality of care. Results revealed that health workers trained in IMCI provided better care than those who were not. It was noted that achieving training coverage alone was not sufficient to improve and sustain quality of care, and other factors such as training quality, effective supervision, drug availability, equipment and government policy were important.

One study in [34], showed that basic health workers were able to correctly case manage sick children and it highlighted that that there should be follow up sessions after the initial training, and regular and frequent follow up by supervisors is important. Provision of supplies such as drugs are necessary for better practice of training in IMCI.

All these studies highlighted the importance of training of MLPs. Moreover, some also mentioned that training in integrated management of infectious diseases is crucial. These studies have combined to give us insight into the effect of training of MLPs.

2.10 Summary

In this Chapter, we gave an overview of the biology and epidemiology of malaria, pneumonia, HIV and TB. We also presented a literature review on mathematical models of malaria, pneumonia, HIV and TB and some literature on training interventions. We noted that there are no models devoted to malaria-pneumonia coinfection and that no models have considered the impact of training interventions, especially for more than one disease.

The ideas provided by the models and training literature we reviewed were useful and informative in our research. We gained lots of insight on how to model all the diseases that we considered.

Chapter 3

IDCAP Data and Performance Indicators

3.1 Introduction

Integrated Infectious Disease Capacity-Building Evaluation (IDCAP) program started in 2009 at 36 sites throughout Uganda. Its focus was to provide an integrated package of infectious disease capacity-building activities at the sites, consisting of a core curriculum of integrated infectious disease training for mid-level practitioners and on-site support for multidisciplinary teams at the clinic level. The aim of the program was to evaluate the impact of training on individual and clinic performance, and to test whether the incremental impact of practical training at the site relative to classroom training alone could be cost-effective.

In this regard, IDCAP carried out two training interventions: Integrated Management of Infectious Diseases (IMID) and On-Site Support Services (OSS), at 36 sites throughout Uganda to improve diagnosis and treatment of infectious diseases [62, 122]. The diseases considered were: malaria, pneumonia, HIV and TB. The sites were grouped into two study arms: Arm A and Arm B. All the sites received IMID and OSS was implemented at Arm A sites for the intervention period.
IMID was classroom based and was given at IDI. OSS was given as a two day practical training at the site every month for a period of nine months. More about the project design and implementation is in [62], IMID and OSS have been described in [122] and TABLE

3.1 gives the sites where the study was carried out.

TABLE. 3.1. Arm A and Arm B sites

Arm A sites	Subcounty population	Arm B sites	Subcounty population
Mukuju	33000	Yumbe	65000
Rugazi	42900	Maracha	27100
Buyinja	57500	Rubaya	35100
Nsinze	23100	Koboko	44500
Kiwangala	46900	Pajule	29000
Kitwe	52300	Mulanda	32300
Rubare	30300	Bukwo	14100
Pakwach	20800	Rukunyu	59400
Midigo	69100	Pallisa	29600
Madi-opei	13300	Kiyunga	35500
Karugutu	21500	Omugo	38100
Ishongororo	44400	Shuuku	23800
Kityerera	75900	Busiu	30800
Butebo	23300	Apapai	31500
Kigezi	16100	Nyimbwa	32700
Mparo	25800	Kojja	66300
Rugarama	11600	Kasangati	74000
Magale	48300	Kisubi	76500

IDCAP evaluated the impact of training of Mid-Level Practitioners (MLPs) using perfomance indicators such as proportion of patients tested, proportion of patients that are prescribed appropriate treatment and those that receive appropriate medication. All the performance indicators are given in subsection 3.2.2.

3.2 IDCAP data and parameters

Data were collected on the performance indicators and on malaria and pneumonia disease cases before the intervention (baseline) and after the intervention (IMID and OSS).

3.2.1 Malaria and pneumonia data

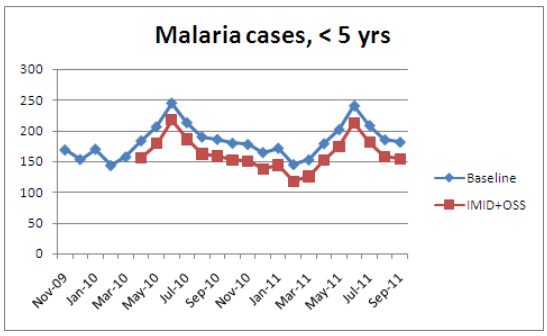
Data on malaria and pneumonia cases were collected from all the 36 sites at baseline for five months and 18 months for IMID and OSS. In our work, we used the average number of malaria and pneumonia cases for an average site considering Arm A sites.

FIG. 3.1(a), FIG. 3.1(b) and FIG. 3.1(c) show the number of malaria cases for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ at baseline and for the two interventions of IMID and combination of IMID and OSS. These are malaria predictions obtained using a linear regression equation and data on number of malaria cases collected from Arm A sites.

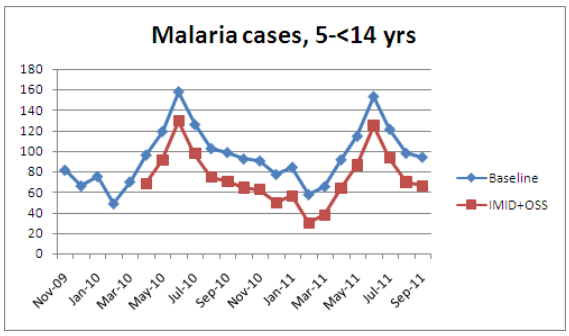
The number of pneumonia cases do not change with time and the baseline value of pneumonia cases for the three age groups, $[0, 5)$, $[5, 14)$ and $[14, 50)$ are given in TABLE. 3.2. TABLE. 3.2 also has proportions of individuals that have severe malaria, severe pneumonia and severe coinfection, and the proportions of symptomatic malaria-pneumonia individuals that recover from malaria-pneumonia coinfection, pneumonia and malaria.

TABLE. 3.2. Number of pneumonia cases at baseline, proportions of individuals with severe malaria-pneumonia coinfection, q, severe pneumonia, q_1 and severe malaria, q_2 and proportion of symptomatic malaria-pneumonia coinfected individuals that recover from malaria-pneumonia coinfection, z, pneumonia, z_1 and malaria, z_2.

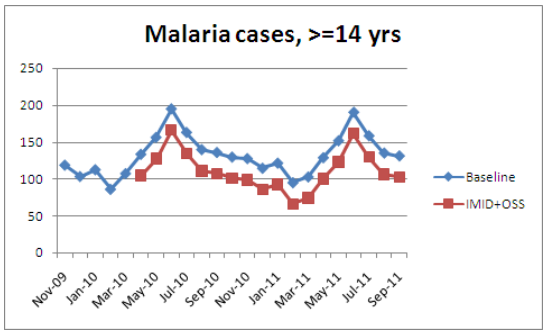
Age group	Pneumonia cases	$q,\ q_1,\ q_2$
< 5	53	$0.279,\ 0.075,\ 0.646$
$5- < 14$	6	$0.03,\ 0.04,\ 0.93$
$>= 14$	24	$0.018,\ 0.066,\ 0.916$
Proportion		
$z = 0.2,\ z_1 = 0.4,\ z_2 = 0.4$		



(a)



(b)



(c)

FIG. 3.1. Unpublished data: malaria cases for baseline, IMID combined with OSS for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ from Arm A

3.2.2 IDCAP performance indicators

The interventions were evaluated by using performance indicators that focused on patient assessment and screening, treatment, prevention and referral and follow up [62]. TABLE 3.3 presents the performance indicators that were considered for malaria, pneumonia, HIV and TB.

3.2.3 Parameters related with the interventions

IDCAP interventions dealt with improvement in patient assessment, patient triage and appropriate drug prescription for patients and this has an effect on the rate of recovery and the rate out of emergency. Thus the parameters that are related to the interventions are: the recovery rate and rate out of emergency.

We describe the general form of the recovery rate in FIG. 3.2.

TABLE. 3.3. IDCAP performance indicators for malaria and pneumonia

Performance indicator
Uncomplicated disease (malaria and pneumonia)
Proportion who were prescribed and received appropriate treatment
Severe disease (malaria and pneumonia)
Proportion triaged
Proportion who were prescribed and received appropriate treatment
HIV
Proportion with an HIV test result
Proportion on ART
Proportion on Cotrimoxazole (CTX)
Proportion of pregnant woment who receive ART on delivery
Proportion of HIV-exposed babies who receive ART on delivery
TB
Proportion who are tested
Proportion who initiated treatment
Proportion that complete treatment
HIV and TB
Proportion with an HIV test result
Proportion on Cotrimoxazole (CTX)
Proportion on ART

Recovery rate

This applies to individuals with uncomplicated disease. It has been divided into six terms based on FIG. 3.2.

Individuals seen at the health centres are the ones that report. The others that do not report may use traditional medicine or may recover naturally. There is evidence that shows that some individuals clear their infection without treatment [144, 145]. We assume that

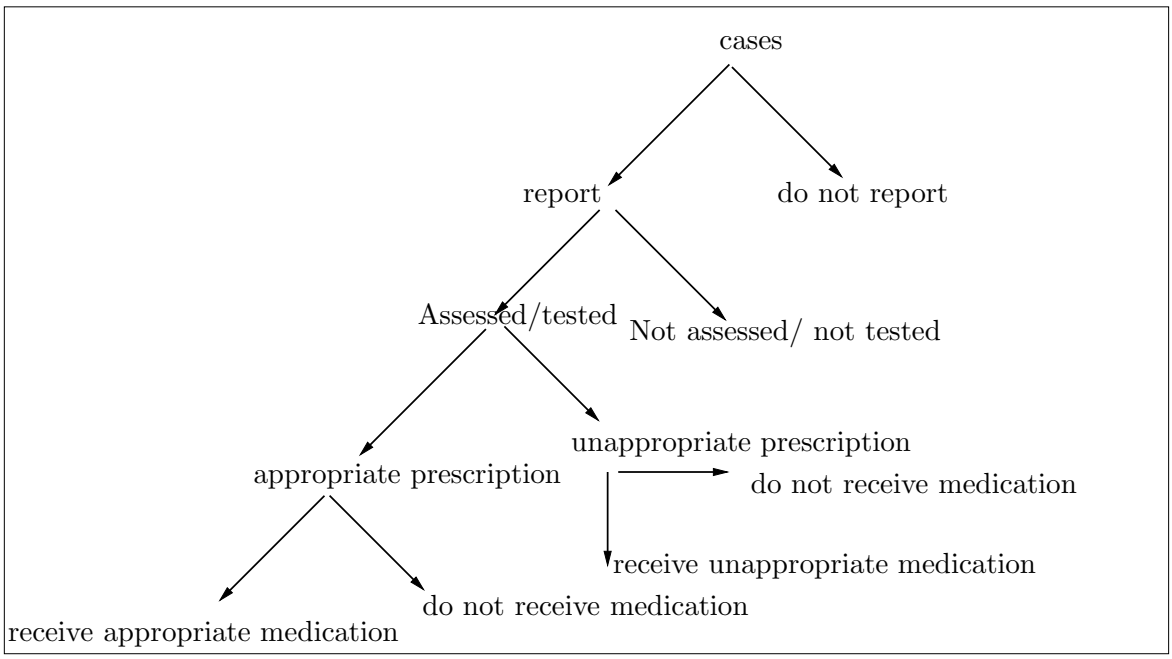


FIG. 3.2. General recovery term

untreated symptomatic infections are cleared in 180 days [26, 59, 151]. We also assume that all individuals with appropriate medication recover and only 62% of those who receive unappropriate medication (assuming 38% resistance to chloroquine [65, 141]), recover from symptomatic malaria.

The terms making up the average recovery term, r are given as

$$r_1 = \text{proportion reporting to clinic} \times \text{proportion assessed/tested} \times \text{proportion with appropriate prescription} \times \text{proportion that receive medication} \times \frac{1}{\text{duration of symptomatic disease with appropriate medication}}$$

$$r_2 = \text{proportion reporting to clinic} \times \text{proportion assessed/tested} \times \text{proportion with appropriate prescription} \times (1 - \text{proportion that receive medication}) \times \frac{1}{\text{duration of symptomatic disease with no medication}}$$

$$r_3 = \text{proportion reporting to clinic} \times \text{proportion assessed/tested} \times (1 - \text{proportion with appropriate prescription}) \times \text{proportion that receive medication} \times \frac{1}{\text{duration of symptomatic disease with inappropriate medication}}$$

$$r_4 = \text{proportion reporting to clinic} \times \text{proportion assessed/tested} \times (1 - \text{proportion with appropriate prescription}) \times (1 - \text{proportion that receive medication}) \times \frac{1}{\text{duration of symptomatic disease with appropriate medication}}$$

$$r_5 = \text{proportion reporting to clinic} \times \text{proportion not assessed/not tested} \times \frac{1}{\text{duration of symptomatic disease with no medication}}$$

$$r_6 = \text{proportion not reporting to clinic} \times \frac{1}{\text{duration of symptomatic disease with no medication}}$$

$$r = r_1 + r_2 + r_3 + r_4 + r_5 + r_6$$

r gives the general recovery rate.

For the recovery rate of malaria, r_M, we do not consider the assessment or tested term. This is because, almost all individuals presenting with fever are presumed to be having malaria and are given malaria medication whether they are tested or not. Thus r_M will contain only five terms.

The recovery rate of pneumonia, $r_{_P}$ also has five terms because we do not consider the assessment term since almost all individuals who present with cough and cold are given antibiotics.

The recovery rate of TB, $r_{_{TB}}$ has all the six terms and in addition to those, the proportion of TB patients who complete treatment is also considered. The proportion of active TB individuals who report to the clinic is very small because there is no active case finding. Moreover, TB patients report to health centres after four months of illness [167, 168]. In [200], the the case detection rate for all TB cases was 38% to 44% from 1995 to 2009. For our model simulations, we take the proportion of TB active individuals reporting as 35% for the $[0, 5)$ age group and 33% for the $[5, 14)$ and $[14, 50)$ age groups.

Rate out of emergency class

This applies to individuals in severe disease class. It depends on the proportion of individuals triaged, those that are prescribed and receive appropriate medication. We assume that if a patient with severe disease fails to access treatment, the patient dies. It is documented that individuals and children with severe malaria or severe pneumonia die within 24 to 48 hours [18, 81, 82, 140, 189]. We take the duration of being an emergency case to be 2 days and we define the rate out of emergency as

$$\begin{aligned} = \ & \text{proportion reporting to clinic} \times \text{proportion triaged} \times \\ & \text{proportion prescribed appropriate treatment} \times \text{proportion who receive treatment} \\ & \times \frac{1}{\text{duration as an emergency case}}. \end{aligned}$$

3.3 Impact of IMID and OSS

To calculate the impact of IMID and the combined intervention of IMID and OSS, we make use of the following formula:

$$\begin{aligned} \text{Indicator after intervention} \ = \ & \text{Indicator before intervention} \times (1 + (\text{Coverage of intervention} \\ & \times \text{Impact of intervention on indicator})) \end{aligned}$$

Suppose that the coverage of the intervention is 100%, the impact of the intervention on the indicator will be given as:

$$\text{Impact of intervention on indicator} = \frac{\text{Indicator after intervention}}{\text{Indicator before intervention}} - 1.$$

The impact of the performance indicators are given in TABLE 3.4 for malaria and pneumonia, TABLE 3.5 for TB and TABLE 3.6 for HIV.

3.3.1 Effect of IMID and OSS

To obtain the effect of IMID, combined intervention of IMID and OSS and the incremental impact of OSS on number of cases, prevalence, incidence and deaths, we put in mind that for a positive effect, there would be a decline in cases, prevalence, incidence and deaths with reference to baseline. Thus for the effect of IMID and IMID+OSS, we calculated the difference between IMID or IMID with OSS values and baseline values and divided by baseline values. The incremental impact of OSS was found by subtracting the IMID with OSS values from IMID ones and dividing by IMID values. The formulas are:

$$\begin{aligned} \text{Effect of IMID} &= (\text{Baseline} - \text{IMID})/\text{Baseline} \\ \text{Effect of IMID+OSS} &= (\text{Baseline} - \text{IMID+OSS})/\text{Baseline} \\ \text{Incremental impact of OSS} &= (\text{IMID} - \text{IMID+OSS})/\text{IMID} \end{aligned} \tag{3.1}$$

However, for indicators such as the number of individuals who are enrolled onto ART and the number of TB patients that recover, there would be an increase in these numbers during the period of the interventions, if we are to have a positive effect. Thus to find the effect of IMID and IMID+OSS, we would reverse equations in 3.1 as:

$$\begin{aligned} \text{Effect of IMID} &= (\text{IMID} - \text{Baseline})/\text{IMID} \\ \text{Effect of IMID+OSS} &= (\text{IMID+OSS} - \text{Baseline})/\text{IMID+OSS} \\ \text{Incremental impact of OSS} &= (\text{IMID+OSS} - \text{IMID})/\text{IMID+OSS} \end{aligned}$$

TABLE. 3.4. Impact of IMID and OSS on malaria and pneumonia indicators as compared to baseline

Indicator	Baseline	IMID	Impact	IMID+OSS	Impact
Coverage of intervention		26%		Estimated	
Non-severe malaria					
< 5 **years**					
Proportion treated appropriately	0.49	0.529	0.0796	0.746	0.522
$>= 5$ **years**					
Proportion treated appropriately	0.41	0.443	0.08	0.624	0.522
Non-severe pneumonia					
< 5 **years**					
Proportion treated appropriately	0.56	0.627	0.12	0.533	−0.048
$>= 5$ **years**					
Proportion treated appropriately	0.51	0.571	0.12	0.486	−0.047
Severe disease					
< 5 **years**					
Proportion triaged	0.26	0.335	0.288	0.53	1.038
Proportion treated appropriately	0.45	0.432	−0.04	0.795	0.77
$>= 5$ **years**					
Proportion triaged	0.27	0.348	0.289	0.55	1.037
Proportion treated appropriately	0.27	0.259	−0.041	0.477	0.77

TABLE. 3.5. Impact of IMID and OSS on parameters for indicators of TB

Indicator	Baseline	IMID	Impact	IMID+OSS	Impact
Coverage of intervention		26%		58%	
$<$ 14 **years**					
Proportion who are tested	0.01	0.012	0.2	0.013	0.3
Proportion who initiated treatment	0.4	0.324	−0.19	0.522	0.305
Proportion that complete treatment	0.41	0.136	−0.668	0.142	−0.654
$>=$ 14 **years**					
Proportion who are tested	0.15	0.18	0.2	0.196	0.307
Proportion who initiated treatment	0.4	0.324	−0.19	0.522	0.305
Proportion that complete treatment	0.41	0.136	−0.668	0.142	−0.654

TABLE. 3.6. Impact of IMID and OSS on HIV indicators

Indicator	Baseline	IMID	Impact	IMID+OSS	Impact
Coverage of intervention		26%		58%	
$<$ 14 **years**					
Proportion with an HIV test result	0.019	0.019	0.0	0.021	0.105
$>=$ 14 **years**					
Proportion with an HIV test result	0.072	0.071	−0.014	0.077	0.069
Pregnant women					
Proportion with an HIV test result	0.67	0.657	−0.019	0.716	0.069
Proportion enrolled into HIV care	0.33	0.406	0.23	0.52	0.576
Proportion eligible on ART	0.9	0.891	−0.01	0.855	−0.05
Proportion on Cotrimoxazole (CTX)	0.91	0.9	−0.011	0.91	0.0
Proportion who receive ART on delivery	0.28	0.266	−0.05	0.25	−0.107
Proportion of HIV-exposed babies who receive ART on delivery	0.75	0.713	−0.049	0.67	−0.107
Proportion of infants enrolled into HIV care	0.44	0.541	0.23	0.693	0.575
Proportion of eligible infants on ART	0.22	0.218	−0.009	0.209	−0.05
TB patients					
Proportion with an HIV test result	0.9	0.954	0.06	0.944	0.049
Proportion enrolled into HIV care	0.3	0.369	0.23	0.472	0.573
Proportion on Cotrimoxazole (CTX)	1.0	0.99	−0.01	1.0	0.0
Proportion eligible on ART	0.72	0.713	−0.01	0.684	−0.05

3.4 Summary

This chapter gives information about IDCAP, the data collected and the performance indicators used to evaluate the two training interventions, IMID and OSS. The impact of the two training interventions on the indicators was calculated and the formula to calculate their effect on cases, deaths, incidence and prevalence was also given. The information in this chapter will be used in later chapters.

Chapter 4

Malaria-Pneumonia Coinfection

4.1 Introduction

In this chapter, we formulate and use a malaria-pneumonia coinfection model to investigate the effect of two training interventions on malaria and pneumonia case management.
The reason for using such a model being that individuals with malaria and pneumonia have overlapping symptoms when severe state and diagnosis of either malaria or pneumonia is difficult. Thus integrated management of both diseases is carried out. The points of interest in the management of malaria and pneumonia cases are appropriate diagnosis, prescription and receiving of treatment.

IDCAP evaluated the effect of IMID and OSS on indicators such as the proportion of malaria and pneumonia patients prescribed appropriate medication, proportion who received appropriate treatment and proportion of patients who were triaged. Using these effects to provide information on incidence, prevalence and mortality of malaria and pneumonia, requires mathematical modelling.

Thus in this chapter, we develop a mathematical model that accounts for the transmission dynamics of malaria and pneumonia for three age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ and investigate the effectiveness of IMID and OSS on management of both diseases.
Because this model uses new malaria and pneumonia sub-models, we will start by formulating these two sub-models and their underlying assumptions. We will also perform mathematical analyses of their dynamical behaviour. Finally, we will merge the two sub-

models into one coinfection model, to which we will add age structure.

4.2 Malaria model

We describe a model of malaria with no age structure. In this model, the population is divided into three classes: susceptibles (S), non-severe symptomatic malaria (M) - uncomplicated malaria with symptoms that are easily manageable and severe malaria ($\widetilde{M}$) - complicated malaria with advanced symptoms (emergency).

We make the following assumptions in the model:

1. We assume that a constant proportion, m of susceptibles always has asymptomatic infection.

2. Deaths of malaria occur only in severe malaria (emergency) class.

In the model, individuals are recruited into the susceptible class at a constant rate, B. Susceptible individuals either move (through infection, reinfection or reactivation) to the non-severe class (at a rate $\lambda_{vh} + \vartheta$) or die at a rate μ. Individuals in the non-severe symptomatic class either recover (at a rate r_{M}), move to severe class at a rate α_{M} or die at a rate μ. Severe malaria individuals either move out of the emergency class at a rate θ_{M} or die at a rate $\mu_{\widetilde{M}}$.

We also have mosquito dynamics with the population of mosquitoes being made up of susceptible, S_{v} and infected mosquitoes, I_{v}. Susceptible mosquitoes are recruited into the population at a rate, b_{v}, are infected with malaria at a rate λ_{hv} and die at rate, μ_{v}. Infected mosquitoes also die at a rate, μ_{v}.

Equations (4.1a)–(4.1c) represent the human population and equations (4.1d)–(4.1e) are for the mosquito population. The model diagram is given by FIG. 4.1 and TABLE 4.1 gives the descriptions of the model variables and parameters.

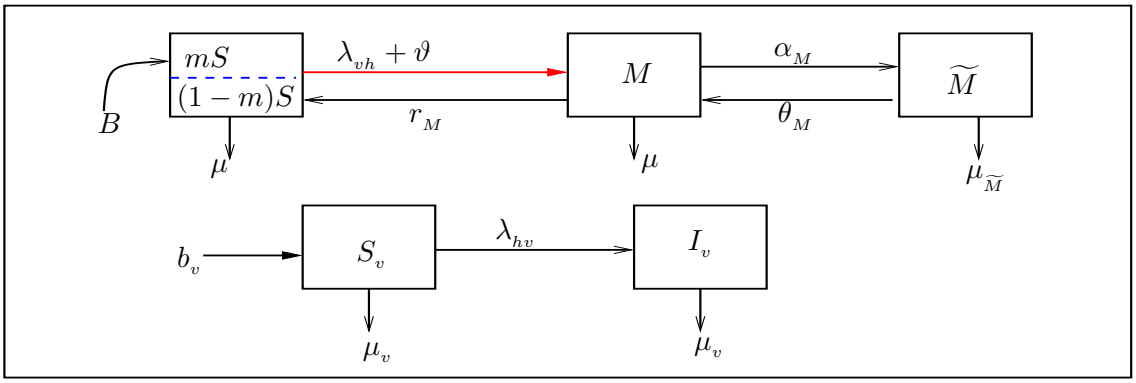


FIG. 4.1. Malaria model

$$\frac{dS}{dt} = B + r_M M - (\lambda_{vh} m' + m\vartheta + \mu)S, \tag{4.1a}$$

$$\frac{dM}{dt} = (\lambda_{vh} m' + m\vartheta)S + \theta_M \widetilde{M} - (r_M + \alpha_M + \mu)M, \tag{4.1b}$$

$$\frac{d\widetilde{M}}{dt} = \alpha_M M - (\theta_M + \mu_{\widetilde{M}})\widetilde{M}, \tag{4.1c}$$

$$\frac{dS_v}{dt} = b_v - \lambda_{hv} S_v - \mu_v S_v, \tag{4.1d}$$

$$\frac{dI_v}{dt} = \lambda_{hv} S_v - \mu_v I_v, \tag{4.1e}$$

where:

(i) $\lambda_{vh} = \beta_{vh} I_v/N$. β_{vh} is the rate at which a vector (mosquito) infects a human, I_v is the infected vector (mosquito) population and N is the human population.

(ii) $m' = m_1(1-m) + m_2 m$. m_1 and m_2 are the proportions of new infections and reinfections that progress to symptomatic disease respectively.

(iii) $\lambda_{hv} = \beta_{hv}(I_M/N)$. β_{hv} is the rate at which a vector (mosquito) becomes infected by biting an infected human. $I_M = M + \widetilde{M} + \zeta_m mS$ is the population of humans with malaria infection where ζ_m is the reduction in infectiousness of individuals with asymptomatic malaria.

The biological feasibility of model system (4.1a)–(4.1e) can be proved in the same way as

TABLE. 4.1. Descriptions of variables and parameters of malaria model.

Variable/Parameter	Description
S	Individuals susceptible to malaria infection or with asymptomatic malaria infection.
M	non-severe malaria individuals.
$\widetilde{M}$	severe malaria individuals.
B	Birth term for humans.
$r_{_M}$	Recovery rate from malaria.
$\lambda_{_{vh}},\ \lambda_{_{hv}}$	Infection terms for malaria.
$\mu,\ \mu_{_{\widetilde{M}}}$	Death rates for susceptible individuals, individuals with symptomatic malaria and those with severe disease.
$\alpha_{_M}$	Rate into severe class.
$\theta_{_M}$	Rate out of severe disease class.
ϑ	Reactivation rate for malaria.
$b_{_v},\ \mu_{_v}$	Birth and death rate for mosquitoes respectively.

will be done for the malaria-pneumonia coinfection model in subsection 4.5.1.

We find the equilibrium points of the malaria sub-model and establish their stability.

4.2.1 Equilibrium points

To get equilibrium points of the malaria model, we set equations (4.1a)–(4.1e) to zero and solve them in terms of the infection terms, λ_{vh} and λ_{hv} of malaria to give

$$S^* = \frac{B(\theta_M(r_M+\mu)+\mu_{\widetilde{M}}(r_M+\alpha_M+\mu))}{\mu r_M(\theta_M+\mu_{\widetilde{M}})+(\mu+m\vartheta+m'\lambda^*_{vh})(\alpha\mu_{\widetilde{M}}+\mu(\theta_M+\mu_{\widetilde{M}}))}, \tag{4.2a}$$

$$M^* = \frac{B(m\vartheta+m'\lambda^*_{vh})(\theta_M+\mu_{\widetilde{M}})}{\mu r_M(\theta_M+\mu_{\widetilde{M}})+(\mu+m\vartheta+m'\lambda^*_{vh})(\alpha\mu_{\widetilde{M}}+\mu(\theta_M+\mu_{\widetilde{M}}))}, \tag{4.2b}$$

$$\widetilde{M}^* = \frac{B\alpha_M(m\vartheta+m'\lambda^*_{vh})}{\mu r_M(\theta_M+\mu_{\widetilde{M}})+(\mu+m\vartheta+m'\lambda^*_{vh})(\alpha\mu_{\widetilde{M}}+\mu(\theta_M+\mu_{\widetilde{M}}))}, \tag{4.2c}$$

$$S^*_v = \frac{b_v}{\lambda^*_{hv}+\mu_v}, \tag{4.2d}$$

$$I^*_v = \frac{b_v\lambda^*_{hv}}{\mu_v(\lambda^*_{hv}+\mu_v)}. \tag{4.2e}$$

Solving λ_{hv} in terms of λ_{vh} and substituting equations (4.2a)–(4.2e) into the force of infection term, λ_{vh} yields

$$A\lambda^{*3}_{vh}+A_1\lambda^{*2}_{vh}+A_2\lambda^*_{vh}+A_3=0, \tag{4.3}$$

where:

$$\begin{aligned}
A &= Bm'^2K^2\mu_v(\beta_{hv}+\mu_v),\\
A_1 &= m'K(-m'b_v\beta_{hv}\beta_{vh}K_1+B\mu_v(\beta_{hv}(K_2+K_3+K_4)+2\mu_vK_5)),\\
A_2 &= -m'b_v\beta_{hv}\beta_{vh}(K_6+K_1K_7)+B\mu_vK_5(m\beta_{hv}K_8+K_5\mu_v),\\
A_3 &= -mb_v\beta_{hv}\beta_{vh}(K_8K_9),
\end{aligned}$$

with

$$\begin{aligned}
K &= \theta_{_M} + \alpha_{_M} + \mu_{\widetilde{M}},\ K_1 = \alpha_{_M}\mu_{\widetilde{M}} + \mu(\theta_{_M} + \mu_{\widetilde{M}}), && (4.4a)\\
K_2 &= (1 + m\zeta_m)r_{_M}(\theta_{_M} + \mu_{\widetilde{M}}),\ K_3 = (2m\vartheta + (1 + m\zeta_m)\mu)(\theta_{_M} + \mu_{\widetilde{M}}), && (4.4b)\\
K_4 &= \alpha_{_M}(2m\vartheta + (1 + m\zeta_m)\mu_{\widetilde{M}}), && (4.4c)\\
K_5 &= (\theta_{_M} + \mu_{\widetilde{M}})(r_{_M} + m\vartheta + \mu) + \alpha_{_M}(m\vartheta + \mu_{\widetilde{M}}), && (4.4d)\\
K_6 &= r_{_M}(\theta_{_M} + \mu_{\widetilde{M}})(\mu(1 + m\zeta_m)(\theta_{_M} + \mu_{\widetilde{M}}) + \alpha_{_M}(\mu + m\zeta_m\mu_{\widetilde{M}})), && (4.4e)\\
K_7 &= (\mu(1 + m\zeta_m) + 2m\vartheta)(\theta_{_M} + \mu_{\widetilde{M}}) + \alpha_{_M}(\mu + 2m\vartheta + m\zeta_m\mu_{\widetilde{M}}), && (4.4f)\\
K_8 &= (\theta_{_M} + \mu_{\widetilde{M}})(\zeta_m r_{_M} + \vartheta + \zeta_m\mu) + \alpha_{_M}(\vartheta + \zeta_m\mu_{\widetilde{M}}), && (4.4g)\\
K_9 &= \mu r_{_M}(\theta_{_M} + \mu_{\widetilde{M}}) + (\mu + m\vartheta)K_1. && (4.4h)
\end{aligned}$$

We then consider two cases, where $m \neq 0$ and $m = 0$.

Case 1: $m \neq 0$

In this case, A_3 is negative, which implies that there is no DFE and there exists at least one positive endemic equilibrium.

Case 2: $m = 0$

$A_3 = 0$ and we have

$$\lambda^*_{vh}(A^*\lambda^{*2}_{vh} + A^*_1\lambda^*_{vh} + A^*_2) = 0, \tag{4.5}$$

where

$$\begin{aligned}
A^* &= Bm_1^2K^2\mu_{_v}(\beta_{_{hv}} + \mu_{_v}),\\
A^*_1 &= m_1K(-m_1b_{_v}\beta_{_{hv}}\beta_{_{vh}}K_1 + B\mu_{_v}(\beta_{_{hv}}(k^*_2 + k^*_3 + k^*_4) + 2\mu_{_v}k^*_5)),\\
A^*_2 &= B\mu_{_v}^2K^{*2}_5(1 - (R_0^M)^2),
\end{aligned}$$

with

$$\begin{aligned}
K^*_2 &= r_{_M}(\theta_{_M} + \mu_{\widetilde{M}}),\ K^*_3 = \mu(\theta_{_M} + \mu_{\widetilde{M}}),\ K^*_4 = \alpha_{_M}\mu_{\widetilde{M}}. && (4.6a)\\
K^*_5 &= \alpha_{_M}\mu_{\widetilde{M}} + (\theta_{_M} + \mu_{\widetilde{M}})(r_{_M} + \mu). && (4.6b)
\end{aligned}$$

and

$$R_0^M = \sqrt{\frac{m_1 b_{_v} \mu \beta_{_{hv}} \beta_{_{vh}} (\theta_{_M} + \alpha_{_M} + \mu_{_{\widetilde{M}}})}{B\mu_{_v}^2 (\alpha_{_M} \mu_{_{\widetilde{M}}} + (\theta_{_M} + \mu_{_{\widetilde{M}}})(r_{_M} + \mu))}}$$

which is the malaria basic reproductive number and it will be discussed in the subsequent subsubsection.

Solving equation (4.5) results into $\lambda_{_{vh}}^* = 0$ which gives the Disease Free Equilibrium (DFE^M) for malaria sub model. The DFE^M is

$$\left(\frac{B}{\mu}, 0, 0, \frac{b_{_v}}{\mu_{_v}}, 0\right).$$

For $\lambda_{_{vh}}^* \neq 0$, we have

$$\lambda_{_{vh}}^* = \frac{-A_1^* \pm \sqrt{A_1^{*2} - 4A^* A_2^*}}{2A^*},$$

there exists a unique positive endemic equilibrium when $R_0^M > 1$.

The equilibrium points calculation has revealed that the malaria model has a DFE^M when $m = 0$ and a unique endemic equilibrium when $R_0^M > 1$. We will determine the local stability of these equilibrium points in later subsubsections.

Malaria basic reproductive number, R_0^M

Generally, the basic reproductive number,

Definition 4.2.1 *R_0 is the mean number of new infections caused by an infected individual introduced into a wholly susceptible population during the individual's infectious period.*

This number gives us an insight on how fast the disease is spreading. $R_0 < 1$ means that on average, an infected individual causes less than one new infected individual over the course of the infectious period and $R_0 > 1$ implies that an infected individual produces more than one new infection. Therefore, the disease will die out when $R_0 < 1$ and it will invade the population with $R_0 > 1$.

For simple cases, R_0 is given by the product of the infection rate and the mean duration of infection [45]. However, in more complex models, it is calculated using the next generation matrix method in [45] given by FV^{-1} where:

i F is the Jacobian matrix, evaluated at the DFE, of the vector field formed by the new infection terms.

ii V is also a Jacobian matrix evaluated at the DFE of the vector field formed by other transfer terms.

In this particular case, we find the basic reproductive number for malaria, R_0^M and this is calculated as follows:

$$\mathscr{F} = \begin{pmatrix} \lambda_{vh} m_1 S \\ 0 \\ \lambda_{hv} S_v \end{pmatrix} \text{ and } \mathscr{V} = \begin{pmatrix} -\theta_{_M} \widetilde{M} + (r_{_M} + \alpha_{_M} + \mu) M \\ -\alpha_{_M} M + (\theta_{_M} + \mu_{\widetilde{M}}) \widetilde{M} \\ \mu_v I_v \end{pmatrix}.$$

Note that $m = 0$ at DFE.
We find the derivatives of $\mathscr{F}$ and $\mathscr{V}$ at DFE.

$$F = \begin{pmatrix} 0 & 0 & m_1 \beta_{vh} \\ 0 & 0 & 0 \\ \frac{b_v \mu \beta_{hv}}{B \mu_v} & \frac{b_v \mu \beta_{hv}}{B \mu_v} & 0 \end{pmatrix}, \quad V = \begin{pmatrix} r_{_M} + \alpha_{_M} + \mu & -\theta_{_M} & 0 \\ -\alpha_{_M} & \theta_{_M} + \mu_{\widetilde{M}} & 0 \\ 0 & 0 & \mu_v \end{pmatrix}.$$

R_0^M is given by the spectral radius of FV^{-1}. Using mathematica software, we obtain

$$R_0^M = \sqrt{\frac{m_1 b_v \mu \beta_{hv} \beta_{vh} (\theta_{_M} + \alpha_{_M} + \mu_{\widetilde{M}})}{B \mu_v^2 (\alpha_{_M} \mu_{\widetilde{M}} + (\theta_{_M} + \mu_{\widetilde{M}})(r_{_M} + \mu))}}.$$

R_0^M is useful in establishing the stability of the DFE^M which is summarised by Theorem 4.2.2

Theorem 4.2.2 *The DFE^M is locally asymptotically stable if $R_0^M < 1$ and unstable if $R_0^M > 1$*

Stability of EEP^M

For the local stability of the EEP^{M}s, we will make use of the centre manifold Theorem from [32] stated in Theorem A.0.1.

We denote the right hand side of system (4.1a)–(4.1e) by $f = (f_1, f_2, f_3)^T$. The DFE^M is shifted to $(0, 0, 0, 0, 0)$.
We consider the case when $R_0^M = 1$ and take β_{vh} to be our bifurcation parameter. It is given as

$$\beta_{vh}^* = \frac{B\mu_v^2(\alpha_M\mu_{\widetilde{M}} + (\theta_M + \mu_{\widetilde{M}})(r_M + \mu_M))}{m_1 b_v \mu \beta_{vh}(\theta_M + \alpha_M + \mu_{\widetilde{M}})}.$$

The linearised system with $\beta_{vh} = \beta_{vh}^*$ has a zero eigenvalue which is simple.
We follow through the steps stated in Theorem A.0.1 to analyse the dynamics of (4.1a)–(4.1e) near $\beta_{vh} = \beta_{vh}^*$ after the DFE^M has been shifted to $(0, 0, 0, 0, 0)$ and in particular to determine the local stability of the endemic equilibria of the system.
We look for the non-zero partial derivatives of f at DFE^M and these are given in A.1. We calculate the value of a and b.

We have,

$$a = \frac{2\mu_v(-B\beta_{hv}\mu_v K + m_1 b_v \beta_{vh}(-\mu\beta_{hv}K + (\alpha_M(\mu - \mu_{\widetilde{M}}) + (\mu - \mu_{\widetilde{M}})(\theta_M + \mu_{\widetilde{M}}))\mu_v))}{B},$$

Since $\mu_{\widetilde{M}} > \mu$, then $a < 0$.

$$b = \frac{m_1\mu b_v K(\beta_{hv} - \mu_v)}{B\mu_v K_9}.$$

Then $b < 0$ if $\beta_{hv} < \mu_v$ and $b > 0$ if $\beta_{hv} > \mu_v$. We establish the following result in Theorem 4.2.3.

Theorem 4.2.3 *i) If $\beta_{hv} < \mu_v$, the model system (4.1a-4.1e) has a positive unstable equilibrium whenever $R_0^M < 1$ but close to 1.*
ii) If $\beta_{hv} > \mu_v$, the model system (4.1a-4.1e) has a unique endemic equilibrium which is locally asymptotically stable whenever $R_0^M > 1$ but close to 1.

This result raises an important point that the persistence and eradication of malaria disease is dependent on two parameters, that is, the death rate of the mosquito and the infection rate from humans to mosquitoes. In particular, eradication would occur if the infection rate of humans to mosquitoes, $\beta_{hv} < \mu_v$.

Note that in our study population, malaria is endemic. Our values for β_{hv} and μ_v are 4 per month and 3.04 per month respectively averaging across the three age groups of $[0, 5)$, $[5, 14)$ and $[14, 50)$.

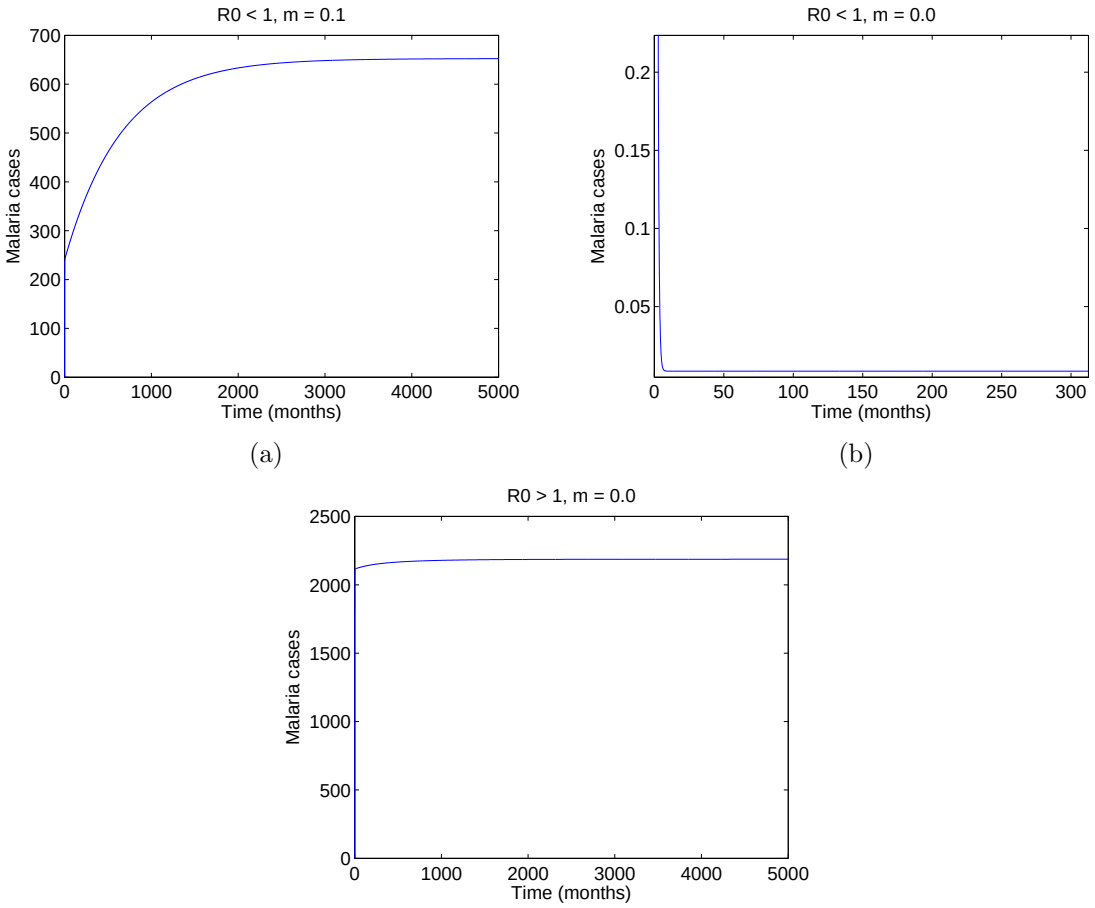


FIG. 4.2. Numerical simulations for R_0^M

FIG. 4.2(a), FIG. 4.2(b) and FIG. 4.2(c) show that for all $m > 0$, there exists an endemic equilibrium irrespective of the value of R_0^M and for $m = 0$, an endemic equilibrium only exists if $R_0^M > 1$.

4.3 Pneumonia model

We describe a model of pneumonia with no age structure. The model is made up of three classes: susceptibles (S), non-severe pneumonia (P) - uncomplicated pneumonia with symptoms that are easily manageable and severe pneumonia ($\widetilde{P}$) - complicated pneumonia with advanced symptoms (emergency). We make the following assumptions:

1. We assume that a constant proportion, p of individuals always has asymptomatic pneumonia infection.
2. Deaths due to pneumonia occur only in severe pneumonia (emergency) class.

Individuals are recruited into the system at a constant rate, B. Susceptibles either get infected, reinfected (at a rate λ_{vh}), reactivate infection (at a rate ω) to move to non-severe symptomatic pneumonia class or die at a rate μ.
Individuals with non-severe symptomatic pneumonia either recover at a rate $r_{_P}$ or develop severe pneumonia at a rate $\alpha_{_P}$ and they die at a rate μ. Those with severe pneumonia recover at a rate $\theta_{_P}$ and die at a rate $\mu_{\widetilde{P}}$. The equations are in (4.7a)–(4.7c), FIG. 4.3 is the model diagram and TABLE. 4.2 gives the definitions of the parameters and variables of pneumonia.

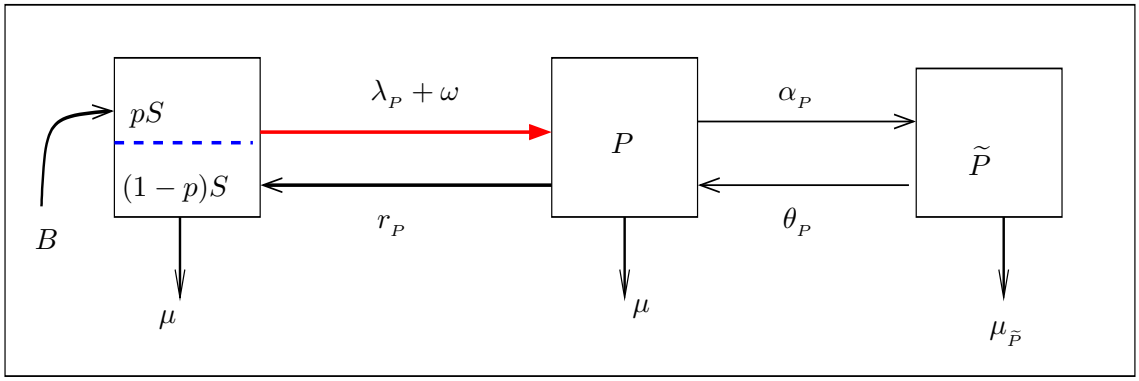


FIG. 4.3. Pneumonia model

$$\frac{dS}{dt} = B + r_{_P}P - (\lambda_{_P}p' + p\omega + \mu)S, \tag{4.7a}$$
$$\frac{dP}{dt} = (\lambda_{_P}p' + p\omega)S + \theta_{_P}\widetilde{P} - (r_{_P} + \alpha_{_P} + \mu)P, \tag{4.7b}$$
$$\frac{d\widetilde{P}}{dt} = \alpha_{_P}P - (\theta_{_P} + \mu_{\widetilde{P}})\widetilde{P}, \tag{4.7c}$$

where

(i) $\lambda_{_P} = \beta_{_p}I_{_P}/N$. $\beta_{_p}$ is the infection rate for pneumonia. $I_{_P} = \zeta_{_p}pS + P + \widetilde{P}$, $N = S + P + \widetilde{P}$. $I_{_P}$ is the infected population, $\zeta_{_p}$ is the reduction in infectiousness of individuals with asymptomatic pneumonia and N is the total population.

(ii) $p' = p_1(1-p) + p_2p$. p_1 and p_2 are the proportions of new infections and reinfections that progress to symptomatic disease respectively.

TABLE. 4.2. Parameters and variables of pneumonia and their descriptions

Variable	Description
S	Individuals susceptible to pneumonia infection or with asymptomatic infection
P	symptomatic individuals
$\widetilde{P}$	severe pneumonia individuals
$r_{_P}$	Recovery rate from pneumonia.
$\lambda_{_P}$	Infection terms for pneumonia.
$\mu,\ \mu_{\widetilde{P}}$	Death rates for susceptible individuals, individuals with symptomatic pneumonia and those with severe pneumonia.
$\alpha_{_P}$	Rate into severe class.
$\theta_{_P}$	Rate out of severe disease class.
ω	Reactivation rate for pneumonia.

The biological feasibility of model system (4.7a)–(4.7c) can be proved in the same way as will be done for the malaria-pneumonia coinfection model in subsection 4.5.1.
We find the equilibrium points of the pneumonia sub-model and establish their stability.

Equilibrium points

To get equilibrium points of pneumonia model, we set equations (4.7a)–(4.7c) to zero and solve them in terms of the infection term of pneumonia, $\lambda_{_P}$, to obtain:

$$S^* = \frac{B(\theta_{_P}(r_{_P}+\mu)+\mu_{\tilde{P}}(r_{_P}+\alpha_{_P}+\mu))}{\mu r_{_P}(\theta_{_P}+\mu_{\tilde{P}})+(\mu+p\omega+p'\lambda^*_{_P})(\alpha_{_P}\mu_{\tilde{P}}+\mu(\theta_{_P}+\mu_{\tilde{P}}))}, \tag{4.8a}$$

$$P^* = \frac{B(p\omega+p'\lambda^*_{_P})(\theta_{_P}+\mu_{\tilde{P}})}{\mu r_{_P}(\theta_{_P}+\mu_{\tilde{P}})+(\mu+p\omega+p'\lambda^*_{_P})(\alpha_{_P}\mu_{\tilde{P}}+\mu(\theta_{_P}+\mu_{\tilde{P}}))}, \tag{4.8b}$$

$$\widetilde{P}^* = \frac{B(\alpha_{_P}(p\omega+p'\lambda^*_{_P})}{\mu r_{_P}(\theta_{_P}+\mu_{\tilde{P}})+(\mu+p\omega+p'\lambda^*_{_P})(\alpha_{_P}\mu_{\tilde{P}}+\mu(\theta_{_P}+\mu_{\tilde{P}}))}, \tag{4.8c}$$

Substituting equations (4.8a)–(4.8c) into the infection term, $\lambda_{_P}$ leads to

$$D\lambda^{*2}_{_P}+D_1\lambda^*_{_P}+D_2=0, \tag{4.9}$$

where:

$$\begin{aligned} D &= p'(\theta_{_P}+\alpha_{_P}+\mu_{\tilde{P}}),\\ D_1 &= ((r_{_P}+\mu)(\theta_{_P}+\mu_{\tilde{P}})+\alpha_{_P}\mu_{\tilde{P}})(1-(1-p)R_0^P)-p(p_2\beta_{_P}+\omega)(\theta_{_P}+\mu_{\tilde{P}}+\alpha_{_P}),\\ D_2 &= -p\beta_{_P}((\theta_{_P}+\mu_{\tilde{P}})(\zeta_{_p}r_{_P}+\omega+\zeta_{_p}\mu)+\alpha_{_P}(\omega+\zeta_{_p}\mu_{\tilde{P}})) \end{aligned}$$

with

$$R_0^P=\frac{p_1\beta_{_P}(\theta_{_P}+\alpha_{_P}+\mu_{\tilde{P}})}{\alpha_{_P}\mu_{\tilde{P}}+(\theta_{_P}+\mu_{\tilde{P}})(r_{_P}+\mu)}$$

which is the basic reproductive number of pneumonia and can be calculated using the next generation matrix as was done for malaria.

Theorem 4.3.1 *i) If $p=0$, then the model system (4.7a)–(4.7c) exhibits a transcritical bifurcation that is when $R_0^P<1$, only the DFE^P exists and is locally asymptotically stable while for $R_0^P>1$, the DFE^P becomes unstable and an EEP exists and is stable.*
ii) If $p\neq 0$, system (4.7a)–(4.7c) has no DFE and has exactly one EEP which is locally asymptotically stable if and only if $R_0^P>1$.

Proof 4.3.1 *We consider two cases*

Case 1: $p=0$

We have:

$$D\lambda_{P}^{*2} + D_1^*\lambda_{P}^* = 0,$$

where

$$D_1^* = (\alpha_{P}\mu_{\tilde{P}} + (\theta_{P} + \mu_{\tilde{P}})(r_{P} + \mu))(1 - R_0^P). \tag{4.10}$$

Solving equation (4.10) gives $\lambda_{P}^* = 0$ *and* $\lambda_{P}^* = \frac{(\alpha_{P}\mu_{\tilde{P}}+(\theta_{P}+\mu_{\tilde{P}})(r_{P}+\mu))(R_0^P-1)}{p_1(\theta_{P}+\alpha_{P}+\mu_{\tilde{P}})}$.

$\lambda_{P}^* = 0$ *yields the DFE*^{P} *for the pneumonia sub-model and it is given as* $\left(\frac{B}{\mu}, 0, 0\right)$.

$\lambda_{P}^* = \frac{(\alpha_{P}\mu_{\tilde{P}}+(\theta_{P}+\mu_{\tilde{P}})(r_{P}+\mu))(R_0^P-1)}{p_1(\theta_{P}+\alpha_{P}+\mu_{\tilde{P}})}$ *gives the EEP which only exists for* $R_0^P > 1$.

Case 2: $p \neq 0$

We have equation (4.9) where D_2 *is negative which implies that the system has no DFE and has exactly one positive endemic equilibrium point.*

EEP^P and its local stability

For the local stability of the EEP^P, we make use of the centre manifold theorem in [32] stated in Theorem A.0.1.
We denote by $f = (f_1, f_2, f_3)^T$, the right hand side of vector field of the system (4.7a)–(4.7c) and shift the DFE^P to $(0, 0, 0)$ by making a change of variables.

We consider the case when $R_0^P = 1$ and we choose β_{P} as our bifurcation parameter. It is given as

$$\beta_{P}^* = \frac{\alpha_{P}\mu_{\tilde{P}} + (\theta_{P} + \mu_{\tilde{P}})(r_{P} + \mu)}{p_1(\theta_{P} + \alpha_{P} + \mu_{\tilde{P}})}.$$

The linearised system with $\beta_{P} = \beta_{P}^*$ has a zero eigenvalue which is simple.
We use Theorem A.0.1 to analyse the dynamics of the modified system near $\beta_{P} = \beta_{P}^*$ and in particular we can determine the local stability of the endemic equilibrium of system (4.7a)–(4.7c).

For computation of a and b, we find the non-vanishing partial derivatives of f at DFE^P.

$$a = -\left(\frac{2p_1\mu\beta_{_P}}{B}\right)\left(\mu\left(\frac{\theta_{_P}\mu+\mu_{_{\tilde{P}}}(\alpha_{_P}+\mu)}{\mu\alpha_{_P}}\right)^2+\frac{2\mu(\theta_{_P}+\mu_{_{\tilde{P}}})}{\alpha_{_P}}\right).$$

Clearly, $a < 0$.

$$b = p1\mu(\frac{\theta_{_P}+\mu_{_{\tilde{P}}}}{\alpha_{_P}}+1).$$

Clearly, $b > 0$.

With $a < 0$ and $b > 0$, there exists a unique endemic equilibrium whenever $R_0^P > 1$ but close to 1 guaranteed by Theorem A.0.1 and it is locally asymptotically stable.

FIG. 4.4(a), FIG. 4.4(b) and FIG. 4.4(c) show that for all $p > 0$, there exists an endemic equilibrium irrespective of the value of R_0^P and for $p = 0$, an endemic equilibrium only exists if $R_0^P > 1$.

4.4 More on mathematical results

Note that our mathematical analysis considers models of one disease and with all the parameters constant. This raises a number of concerns: are the insights we obtain and the inferences we make relevant to our coinfection model with a time dependent parameter? Suppose we study the malaria model with a time dependent mosquito birth rate, would the mathematical results obtained for the constant case be related to that of the time dependent case? Is the basic reproductive number still relevant and if not, is there its equivalent for a model with a time dependent parameter? What about the long term behaviour of such a system? We give a brief discussion on some of these concerns.

The mathematical analysis of models with time dependent parameters has not been explored greatly. There is need to develop threshold values such as the basic reproductive number for the case of non-autonomous systems. In [32], only the upper and lower limits

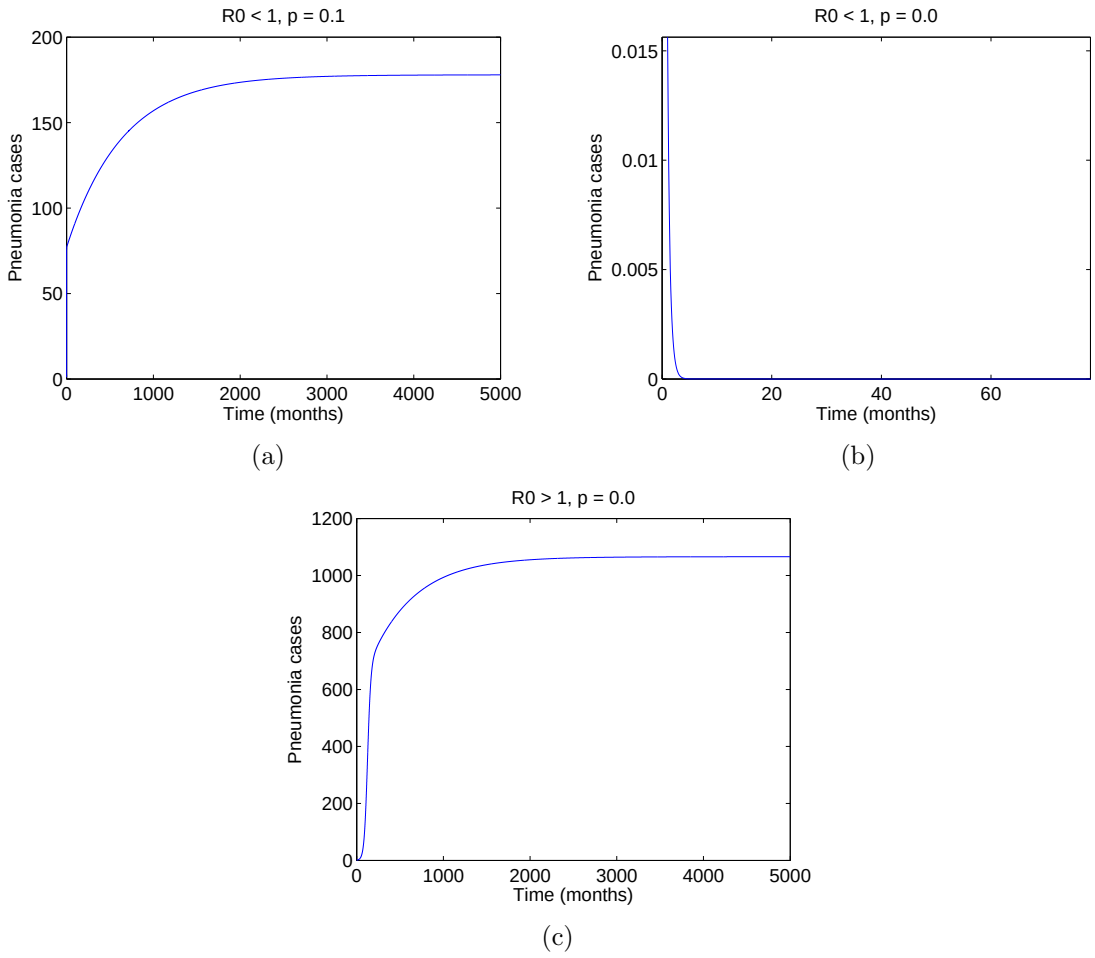


FIG. 4.4. Numerical simulations for R_0^P

for the persistence and eradiction of TB could be calculated. The results for the non-autonomous system in [32] showed that when the parameters were taken to be constant, the reproductive number obtained for elimination and that obtained for persistance were equal to the basic reproduction number for the model with constant parameters. Thus thresholds obtained for persistence and elimination of disease can help shed light on the long time behaviour of models with time dependent parameters.

For our system, the long term behaviour of the system with a time dependent parameter would depend on the asymptotic property of the mosquito birth rate, b_v. A theorem is given in [32] that helps characterize that kind of behaviour. It provides conditions for differentiation of the two important biological states: disease elimination or persistence for a non-autonomous system. Further, it is recommended in [32] that the method of averages

by Ma et al [210] could be used to find sharp threshold conditions.

Considering time periodic models, [9, 84, 210] explain the meaning of the basic reproductive number. In [84], a new definition of R_0 based on the generation evolution operator (GEO), with intuitive clear biological meaning is introduced. The analysis in [84] shows that the spectral radius of GEO equals the spectral radius of the next generation operator, thus it gives the basic reproduction number. Further, a weak sign relation is proved which shows that if the average Malthusian parameter exists, it is nonnegative when $R_0 > 1$ and it is nonpositive when $R_0 < 1$.
In [9], the basic reproductive number, R_0, is the asymptotic ratio of total births in two successive generations of the family tree in demography. In epidemiology, it is defined as the asymptotic ratio of total infections in two successive generations of the infection tree.

In conclusion, our time dependent and periodic models can be studied and their long term behaviour analysed using insights from the articles we have discussed. Note that though we did not carry out this analysis, using time dependent models was a useful way of connecting the parameters in our model to data.

4.5 Malaria-pneumonia coinfection model

We present a mathematical model of malaria and pneumonia coinfection without age structure in this section. It is a combination of the malaria sub-model in section 4.2 and the pneumonia sub-model in section 4.3. It is presented for purposes of clarification and as a tool to understand the coinfection model of malaria and pneumonia with age structure. We neither perform any mathematical analyses on it nor do we run numerical simulations for it.

The malaria-pneumonia coinfection model without age structure comprises five classes: Susceptibles (S), non-severe symptomatic malaria (M), non-severe symptomatic pneumonia (P), non-severe symptomatic malaria-pneumonia coinfection (PM) and the severe disease class ($\widetilde{PM}$).
The severe disease class represents individuals with severe malaria, severe pneumonia and severe malaria-pneumonia coinfection. We have combined the severe classes, for simplicity

and also because the symptoms of severe malaria and severe pneumonia overlap [16, 20, 99] and individuals with either disease in severe cases are treated for both diseases.

The assumptions we used in the malaria and pneumonia sub models still hold in that susceptible class comprises proportions, m and p of individuals with asymptomatic malaria and pneumonia infection respectively and malaria and pneumonia induced deaths occur in the severe (emergency) class only.

In the model, individuals are recruited into the system at a constant rate, B. Susceptible individuals develop symptomatic disease by infection and reinfection (terms λ_{P} and λ_{vh}) and also by reactivation at rates ω and ϑ for pneumonia and malaria respectively and they die at a rate μ.

Symptomatic pneumonia, malaria and coinfected individuals recover at rates r_{P} and r_{M} and r_{PM}. Individuals in PM class are divided into three proportions, z, z_1 and z_2 to represent those who recover from the symptomatic malaria-pneumonia coinfection, pneumonia and malaria respectively. $z + z_1 + z_2 = 1$. Symptomatic pneumonia, malaria and coinfected individuals become severe cases at rates α_{P}, α_{M} and α_{PM} accordingly, move out of the severe class at a rate θ and die at a rate μ.

The severe class, $\widetilde{PM}$ is divided into three proportions: q represents severe malaria-pneumonia coinfection, q_1 is for severe pneumonia and q_2 is for severe malaria. $q+q_1+q_2 = 1$. Individuals with severe disease die at a rate $\mu_{\widetilde{PM}}$ and it is a combination of the death rate of severe malaria, severe pneumonia and severe malaria-pneumonia. Note that these death rates are summation of the disease specific rates and the natural death rate, μ.

We also have mosquito dynamics with the population of mosquitoes being made up of susceptible and infected mosquitoes. They are recruited into the population at a rate, b_v, are infected with malaria at a rate λ_{hv} and die at a rate, μ_v.

The model equations are given by (4.11a)–(4.11g). Equations (4.11a)–(4.11e) are for the human population and equations (4.11f) and (4.11g) represent the mosquito population. FIG. 4.5 is the model diagram and TABLE 4.3 gives a summary of the descriptions of the variables and some parameters for the coinfection. Note that some of the descriptions of variables and parameters are already given in TABLE 4.1 and TABLE 4.2.

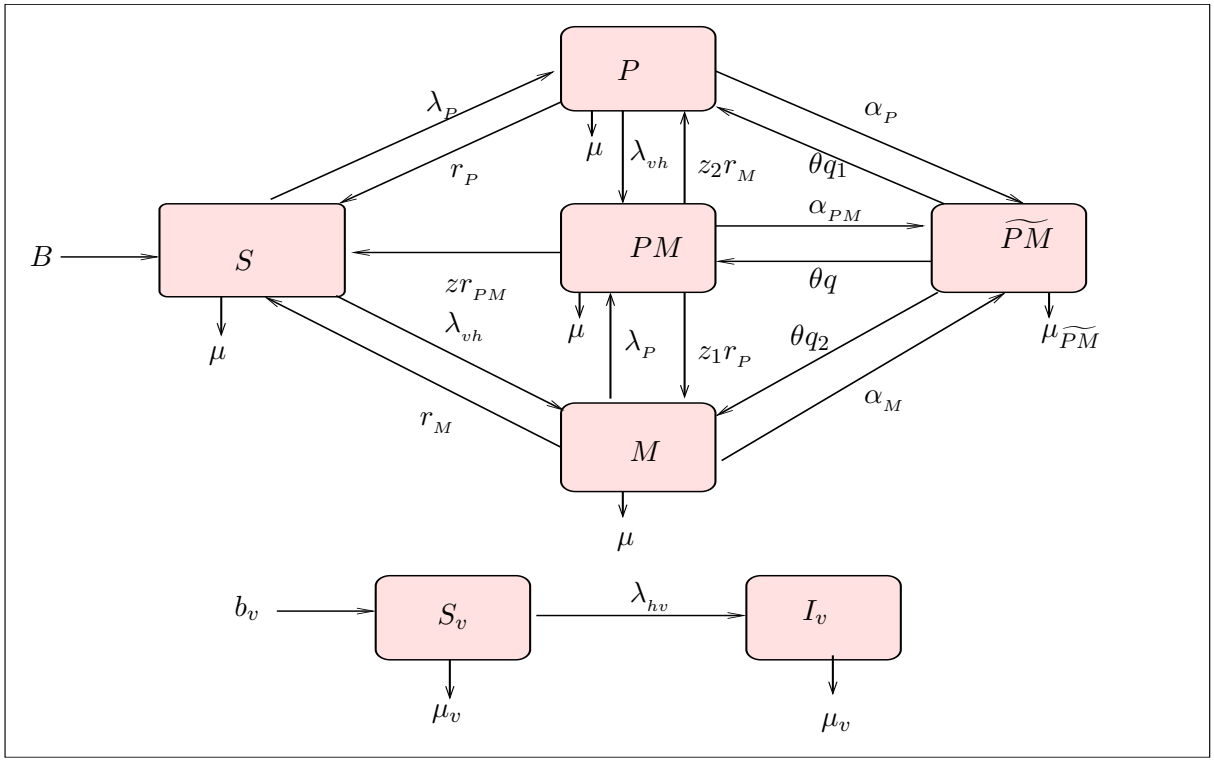


FIG. 4.5. Non age structured malaria-pneumonia coinfection model

$$\begin{aligned}
\frac{dS}{dt} &= B + r_{_P}P + r_{_M}M + zr_{_{PM}}PM - (\lambda_{_P}p' + p\omega + \lambda_{_{vh}}m' + m\vartheta)S && (4.11a)\\
&\quad -\mu S,\\
\frac{dP}{dt} &= (\lambda_{_P}p' + p\omega)S + z_2 r_{_M}PM + \theta q_1\widetilde{PM} - (\lambda_{_{vh}}m' + m\vartheta + r_{_P})P && (4.11b)\\
&\quad -(\alpha_{_P} + \mu)P,\\
\frac{dM}{dt} &= (\lambda_{_{vh}}m' + m\vartheta)S + z_1 r_{_P}PM + \theta q_2\widetilde{PM} - (\lambda_{_P}p' + p\omega + r_{_M})M && (4.11c)\\
&\quad -(\alpha_{_M} + \mu_{_M})M,\\
\frac{dPM}{dt} &= (\lambda_{_P}p' + p\omega)M + (\lambda_{_{vh}}m' + m\vartheta)P + \theta q\widetilde{PM} - (zr_{_{PM}} + z_1 r_{_P})PM && (4.11d)\\
&\quad -(z_2 r_{_M} + \alpha_{_{PM}} + \mu_{_{PM}})PM,\\
\frac{d\widetilde{PM}}{dt} &= \alpha_{_P}P + \alpha_{_M}M + \alpha_{_{PM}}PM - (\theta + \mu_{_{\widetilde{PM}}})\widetilde{PM}, && (4.11e)\\
\frac{dS_{_v}}{dt} &= b_v - (\lambda_{_{hv}} + \mu_{_v})S_{_v}, && (4.11f)\\
\frac{dI_{_v}}{dt} &= \lambda_{_{hv}}S_{_v} - \mu_{_v}I_{_v}, && (4.11g)
\end{aligned}$$

where:

(i) $\lambda_{_{vh}} = \beta_{_{vh}}I_v/N$. $\beta_{_{vh}}$ is the rate at which a vector (mosquito) infects a human, I_v is the infected vector (mosquito) population and N is the human population.

(ii) $m' = m_1(1-m) + m_2 m$. m_1 and m_2 are the proportions of new infections and reinfections that progress to symptomatic disease respectively.

(iii) $\lambda_{_{hv}} = \beta_{_{hv}}(I_{_M}/N)$. $\beta_{_{hv}}$ is the rate at which a vector (mosquito) becomes infected by biting an infected human and $I_{_M} = \zeta_{_m}mS + M + PM + (q+q_2)\widetilde{PM}$ is the population of humans with malaria infection.

(iv) $\lambda_{_P} = \beta_{_p}I_{_P}/N$. $\beta_{_p}$ is the infection rate for pneumonia. $I_{_P} = \zeta_{_p}pS + P + PM + (q + q_1)\widetilde{PM}$ is the population of individuals infected with pneumonia.

(v) $p' = p_1(1-p) + p_2 p$. p_1 and p_2 are the proportions of new infections and reinfections that progress to symptomatic pneumonia disease respectively.

TABLE. 4.3. Variables, parameters for malaria-pneumonia coinfection model and their descriptions

Variable/Parameter	Description
S	Individuals susceptible to malaria or pneumonia infection and those with asymptomatic malaria or pneumonia infection
PM	symptomatic malaria-pneumonia individuals
$\widetilde{PM}$	Individuals with severe malaria, severe pneumonia or severe malaria-pneumonia disease.
$r_{_{PM}}$	Recovery rate for malaria-pneumonia coinfection disease
$\alpha_{_{PM}}$	Rate at which malaria-pneumonia coinfected individuals move to severe class
θ	Rate out of severe disease class
$\mu_{_{\widetilde{PM}}}$	Death rate for severe disease
$q,\ q_1,\ q_2$	Proportions of individuals with severe malaria-pneumonia coinfection, severe pneumonia and severe malaria respectively.
$z,\ z_1,\ z_2$	Proportions of individuals with malaria-pneumonia coinfection who move to susceptible, malaria and pneumonia classes respectively after recovery from the coinfection, pneumonia and malaria accordingly.

4.5.1 Positivity and boundedness of solutions

For biological feasibility of system (4.11a)–(4.11g), it is important that all variables stay positive at all times and as such we analyse this system in the region

$$\Omega = \left\{ (S, P, M, PM, \widetilde{PM}, S_v, I_v) \in \Re_+^7 : S + P + M + PM + \widetilde{PM} \leq \frac{B}{\mu},\ S_v + I_v \leq \frac{b_v}{\mu_v} \right\}.$$

Solutions of the system, remain positive for all time $t \geq 0$ and are bounded in Ω.

Proposition 4.5.1 *System (4.11a)–(4.11g) has for each positive initial condition, a unique solution that is positive. Moreover, the region Ω is positively invariant.*

Proof. Let $S(0), P(0), M(0), PM(0), \widetilde{PM}(0), S_v(0), I_v(0)$ be positive initial conditions and $t_1 = \sup\{t > 0 : S(\tau) > 0,\ P(\tau) > 0,\ M(\tau) > 0,\ PM(\tau) > 0,\ \widetilde{PM}(\tau) > 0,\ S_v(\tau) > 0,\ I_v(\tau) > 0, \text{for all } \tau \in [0, t]\}$.
Since $S(0) \geq 0, P(0) \geq 0, M(0) \geq 0, PM(0) \geq 0, \widetilde{PM}(0) \geq 0, S_v(0) \geq 0, I_v(0) \geq 0$, thus $t_1 > 0$. If $t_1 < \infty$, then necessarily S or P or M or PM or $\widetilde{PM}$ is equal to zero at t_1. Using the variation of constants formula, we have:

$$\begin{aligned} S(t_1) &= S(0)\exp[-\int_0^{t_1}(\lambda_1+\mu)(s)ds] \\ &\quad + \int_0^{t_1}(B + r_P P + r_M M + z r_{PM} PM)\exp[-\int_s^{t_1}(\lambda_1+\mu)(\tau)d\tau]ds. \end{aligned}$$

where $\lambda_1 = \lambda_P p' + p\omega + \lambda_{vh} m' + m\vartheta$.
Moreover, since all the variables are positive in $[0, t_1]$, then $S(t_1) > 0$. It can be shown in a similar way that $P(t_1) > 0,\ M(t_1) > 0,\ PM(t_1) > 0,\ \widetilde{PM}(t_1) > 0$ and $I_v(t_1) > 0$ which is a contradiction. Hence $t_1 = \infty$.

For the invariance of Ω, we add the equations of system (4.11a)–(4.11e) for the human population to obtain:

$$\frac{dN(t)}{dt} = B - \mu(PM + P + M + S) - \mu_{\widetilde{PM}}\widetilde{PM}.$$

Since the solution is positive and $\mu_{\widetilde{PM}} > \mu$, then

$$\frac{dN(t)}{dt} \leq B - \mu N(t).$$

Therefore, $N(t) \leq N(0)e^{-\mu t} + \frac{B}{\mu}(1 - e^{-\mu t})$ and if $N(0) \leq \frac{B}{\mu}$ then so is $N(t)$. Moreover, whenever $N(t) > \frac{B}{\mu}$, $N(t)' < 0$.

For the mosquito population

$$\frac{dN_v(t)}{dt} = b_v - \mu_v N_v.$$

Therefore, $N_v(t) \leq N_v(0)e^{-\mu_v t} + \frac{b_v}{\mu_v}(1 - e^{-\mu_v t})$ and if $N_v(0) \leq \frac{b_v}{\mu_v}$ then so is $N_v(t)$. Moreover, whenever $N_v(t) > \frac{b_v}{\mu_v}$, $N_v(t)' < 0$. Thus every solution of the model equations (4.11a)–(4.11g) with initial conditions in $\mathbb{R}^7_+$ approaches and stays in Ω as $t \to \infty$.

Having shown that the coinfection model with no age-structure is biologically feasible, the biological feasibility of the sub models of malaria and pneumonia can be shown in the same way.

4.6 Age structured malaria-pneumonia model

The coinfection model with age structure is an extension of the model without age structure in section 4.5. It is made up of three age groups, $[0,5)$, $[5,14)$ and $[14,50)$ and these are represented by subscript $j = c, b, a$ on the variables and parameters. Individuals age from one age group to the next at a rate $\eta_i,\ i = 1,2,3$.
All the other definitions of variables and parameters stay the same as explained in section 4.5 with a subscript c, b or a to represent which age group the variable or parameter is in.

The mosquito dynamics are as before except that we have different infection rates for the different age groups.
Model equations are given by (4.12a)–(4.12e) for the $[0,5)$ age group, (4.13a)–(4.13e) for the $[5,14)$ age group, (4.14a)–(4.14e) for the $[14,50)$ age group and (4.15a)–(4.15b) for mosquito dynamics. The model diagram is given by FIG. 4.6.

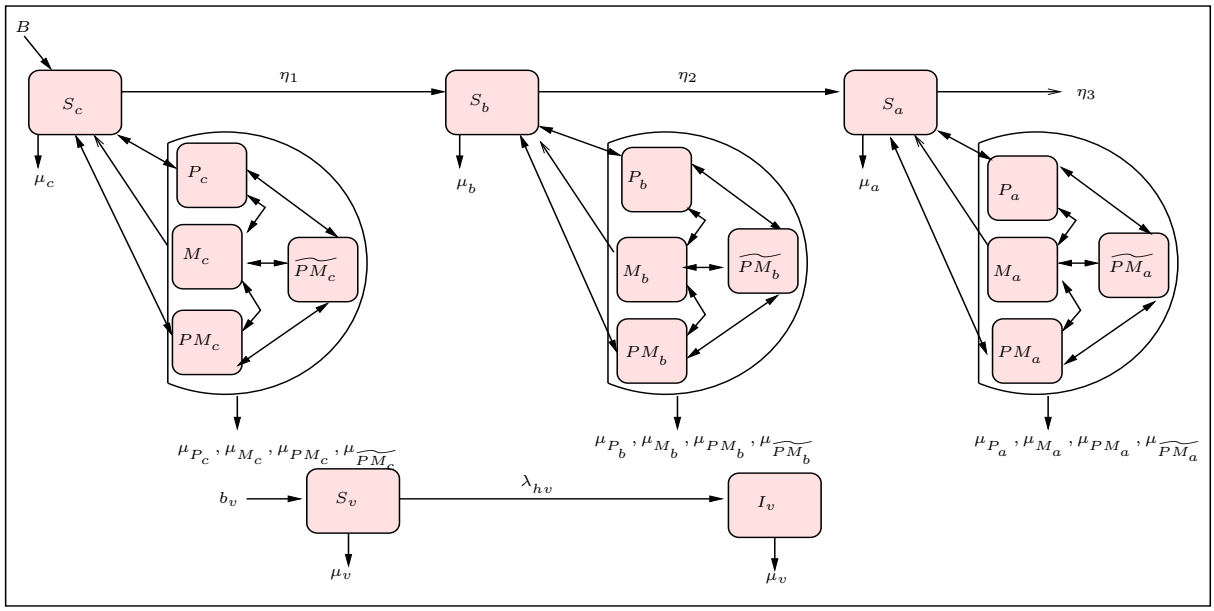


FIG. 4.6. Malaria and pneumonia co-infection model

Equations for $[0,5)$ age group

$$\begin{aligned}
\frac{dS_c}{dt} &= B + r_{P_c}P_c + r_{M_c}M_c + z_c r_{PM_c}PM_c - (\lambda_{P_c}p'_c + p_c\omega_c + \lambda_{vh_c}m'_c)S_c \quad (4.12a)\\
&\quad -(m_c\vartheta_c + \mu_c + \eta_1)S_c,\\
\frac{dP_c}{dt} &= (\lambda_{P_c}p'_c + p_c\omega_c)S_c + z_{2c}r_{M_c}PM_c + \theta_c q_{1c}\widetilde{PM_c} - (\lambda_{vh_c}m'_c + m_c\vartheta_c)P_c \quad (4.12b)\\
&\quad -(r_{P_c} + \alpha_{P_c} + \mu_{P_c} + \eta_1)P_c,\\
\frac{dM_c}{dt} &= (\lambda_{vh_c}m'_c + m_c\vartheta_c)S_c + z_{1c}r_{P_c}PM_c + \theta_c q_{2c}\widetilde{PM_c} - (\lambda_{P_c}p'_c + p_c\omega_c)M_c \quad (4.12c)\\
&\quad -(r_{M_c} + \alpha_{M_c} + \mu_{M_c} + \eta_1)M_c,\\
\frac{dPM_c}{dt} &= (\lambda_{P_c}p'_c + p_c\omega_c)M_c + (\lambda_{vh_c}m'_c + m_c\vartheta_c)P_c + \theta_c q_c\widetilde{PM_c} - z_{1c}r_{P_c}PM_c \quad (4.12d)\\
&\quad -(z_{2c}r_{M_c} + z_c r_{PM_c} + \alpha_{PM_c} + \mu_{P_c} + \eta_1)PM_c,\\
\frac{d\widetilde{PM_c}}{dt} &= \alpha_{P_c}P_c + \alpha_{M_c}M_c + \alpha_{PM_c}PM_c - (\theta_c + \mu_{\widetilde{PM_c}} + \eta_1)\widetilde{PM_c}, \quad (4.12e)
\end{aligned}$$

Equations for $[5,14)$

$$\begin{aligned}
\frac{dS_b}{dt} &= \eta_1 S_c + r_{P_b}P_b + r_{M_b}M_b + r_{PM_b}PM_b - (\lambda_{P_b}p'_b + p_b\omega_b + \lambda_{vh_b}m'_b)S_b \quad (4.13a)\\
&\quad -(m_b\vartheta_b + \mu_b + \eta_2)S_b,\\
\frac{dP_b}{dt} &= \eta_1 P_c + (\lambda_{P_b}p'_b + p_b\omega_b)S_b + z_{2b}r_{M_b}PM_b + \theta_{1b}q_{1b}\widetilde{PM_b} - (\lambda_{vh_b}m'_b)P_b \quad (4.13b)\\
&\quad -(m_b\vartheta_b + \alpha_{P_b} + \mu_{P_b} + \eta_2)P_b,\\
\frac{dM_b}{dt} &= \eta_1 M_c + (\lambda_{vh_b}m'_b + m_b\vartheta_b)S_b + z_{1b}r_{P_b}PM_b + \theta_{2b}q_{2b}\widetilde{PM_b} - \lambda_{P_b}p'_b M_b \quad (4.13c)\\
&\quad -(p_b\omega_b + r_{M_b} + \alpha_{M_b} + \mu_{P_b} + \eta_2)M_b,\\
\frac{dPM_b}{dt} &= \eta_1 PM_c + (\lambda_{P_b}p'_b + p_b\omega_b)M_b + (\lambda_{vh_b}m'_b + m_b\vartheta_b)P_b + \theta_b q_b\widetilde{PM_b} \quad (4.13d)\\
&\quad -(z_{1b}r_{P_b} + z_{2b}r_{M_b} + z_b r_{PM_b} + \alpha_{PM_b} + \mu_{P_b} + \eta_2)PM_b,\\
\frac{d\widetilde{PM_b}}{dt} &= \eta_1\widetilde{PM_c} + \alpha_{P_b}P_b + \alpha_{M_b}M_b + \alpha_{PM_b}PM_b - (\theta_b + \mu_{\widetilde{PM_b}} + \eta_2)\widetilde{PM_b}, \quad (4.13e)
\end{aligned}$$

Equations for $[14, 50)$

$$\begin{aligned}
\frac{dS_a}{dt} &= \eta_2 S_b + r_{P_a} P_a + r_{M_a} M_a + r_{PM_a} PM_a - (\lambda_{P_a} p'_a + p_a\omega_a)S_a \qquad (4.14a)\\
&\quad -(\lambda_{vh_a} m'_a + m_a\vartheta_a + \mu_a + \eta_3)S_a,\\
\frac{dP_a}{dt} &= \eta_2 P_b + (\lambda_{P_a} p'_a + p_a\omega_a)S_a + z_{2a} r_{M_a} PM_a + \theta_{1a} q_{1a}\widetilde{PM_a} \qquad (4.14b)\\
&\quad -(\lambda_{vh_a} m'_a + m_a\vartheta_a + \alpha_{P_a} + \mu_{P_a} + \eta_3)P_a,\\
\frac{dM_a}{dt} &= \eta_2 M_b + (\lambda_{vh_a} m'_a + m_a\vartheta_a)S_a + z_{1a} r_{P_a} PM_a + \theta_{2a} q_{2a}\widetilde{PM_a} \qquad (4.14c)\\
&\quad -(\lambda_P p'_a + p_a\omega_a + r_{M_a} + \alpha_{M_a} + \mu_{P_a} + \eta_3)M_a,\\
\frac{dPM_a}{dt} &= \eta_2 PM_b + (\lambda_{P_a} p'_a + p_a\omega_a)M_a + (\lambda_{vh_a} m'_a + m_a\vartheta_a)P_a + \theta_a q_a\widetilde{PM_a} \qquad (4.14d)\\
&\quad -(z_{1a} r_{P_a} + z_{2a} r_{M_a} + z_a r_{PM_a} + \alpha_{PM_a} + \mu_{P_a} + \eta_3)PM_a,\\
\frac{d\widetilde{PM_a}}{dt} &= \eta_2\widetilde{PM_b} + \alpha_{P_a} P_a + \alpha_{M_a} M_a + \alpha_{PM_a} PM_a - (\theta_a + \mu_{\widetilde{PM_a}} + \eta_3)\widetilde{PM_a}. \qquad (4.14e)
\end{aligned}$$

The mosquito dynamics are given by

$$\begin{aligned}
\frac{dS_v}{dt} &= b_v - (\lambda_{hv_c} + \lambda_{hv_b} + \lambda_{hv_a})S_v - \mu_v S_v, \qquad (4.15a)\\
\frac{dI_v}{dt} &= (\lambda_{hv_c} + \lambda_{hv_b} + \lambda_{hv_a})S_v - \mu_v I_v, \qquad (4.15b)
\end{aligned}$$

where:

(i) $\lambda_{vh_c} = \beta_{vh_c} I_v/N$, $\lambda_{vh_b} = \beta_{vh_b} I_v/N$, $\lambda_{vh_a} = \beta_{vh_a} I_v/N$. β_{vh_c}, β_{vh_b}, β_{vh_a} are the rates at which a vector (mosquito) infects an individual in the $[0, 5)$, $[5, 14)$, $[14, 50)$ age groups respectively. I_v is the infected vector (mosquito) population and N is the human population.

(ii) For the $[0, 5)$ age group, $m'_c = m_{1c}(1 - m_c) + m_{2c}m_c$. m_{1c} and m_{2c} are the proportions of new infections and reinfections that progress to symptomatic disease respectively. The same definitions hold for the $[5, 14)$ and $[14, 50)$ age groups which are represented by subscripts b and a accordingly.

(iii) $\lambda_{hv_c} = \beta_{hv_c}(I_M/N)$. β_{hv_c} is the rate at which a vector (mosquito) becomes infected by biting an infected human in the $[0, 5)$ age group. $I_M = \sum_{j=c,b,a} \zeta_m m_j S_j + M_j + PM_j + (q_j + q_{2j})\widetilde{PM_j}$ is the population of humans with malaria infection. The same definitions hold for the $[5, 14)$ and $[14, 50)$ age groups which are represented by subscripts b and a in turn.

We use this age structured malaria-pneumonia coinfection model to generate the numerical simulations we present in this chapter.

4.7 Parameters from literature

In addition to parameters obtained using IDCAP data, we also get parameters from literature. In this section, we describe and give information about parameter values and their source. The parameters are displayed in TABLE. 4.4 and TABLE. 4.5. Most of the rates will be given in units of years, a few in months and some in days. However, all the model simulations are run using the time unit of months.

4.7.1 Birth rate

We use demographical data for Uganda: according to the 2000/2001 census, the crude birth rate of Uganda was 47.3 per 1000 [148] and in the 2005/2006, it was 41 per 1000 [149].

Uganda has a young population with approximately 50% of its population being under 15 years of age [85]. Therefore, a model with a density dependent birth term and realistic aging rates would represent its demography well. It would show a population growing exponentially which is representative of Uganda's population for the last two decades up-to-date. However, when disease dynamics are incorporated, using such a model would also show an exponential growth in the number of disease cases. To avoid this, we use a model with a constant birth term and choose appropriate aging, birth and death rates to obtain a realistic age structure.

4.7.2 Natural death rates

We calculated natural death rates using population numbers from Spectrum (DemProj) [87] with default Uganda country data. Probabilities of dying in different age groups in the years 2009 to 2011 were obtained (Number of deaths within an age group in a particular year/Population of age group in that year). Using these probabilities, the rates of death for the years under consideration were calculated using formulas in [61, 124]. We took the average death rates, considering the years 2009 to 2011, and these were given as $\mu_c = 0.026$, $\mu_b = 0.004$ and $\mu_a = 0.008$ for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively.

4.7.3 Aging rates

The age distribution of Uganda is about 19% for $[0, 5)$, 27% for $[5, 14)$ and 54% for $[14, 50)$ [85]. To reflect this age structure, we adopted the following aging rates: 0.19 for $[0, 5)$, 0.13 for $[5, 14)$ and 0.057 for $[14, 50)$.

4.7.4 Parameters of malaria

Mosquito birth rate

This is time dependent to account for the change in the number of mosquitoes born in the different seasons which in turn accounts for the number of malaria cases seen at health facilities.

We estimate four values for the mosquito birth rate using 23 months of data available (refer to subsection 3.2.1) and then use a periodic function which considers the averages of the first two low ones and the first two peak ones afterwards. The absolute numbers of mosquitoes born are given by b_0, b_1, b_2 and b_3 in TABLE. 4.6 and the ones after, b_4 is the average of b_0 and b_2 and b_5 is the average of b_1 and b_3 and then have a repetition, with $b_6 = b_4$.

When changing the values of the mosquito birth rate, we make use of a function that joins two values smoothly. Suppose the number of mosquitoes born changes from value b_j to

value b_{j+1}, then the function is given by

$$f(t) = b_0 + \sum_{j=0}^{5} \frac{(b_{j+1} - b_j)e^{-k_s(t-\tau_j)}}{e^{k_s(t-\tau_j)} + e^{-k_s(t-\tau_j)}},$$

where t is the time, k_s is parameter that determines the slope and τ_j is the time point at which the value changes from b_j to b_{j+1}.

The times (in months) at which one value changes to another are given by τ_0, τ_1, τ_2, τ_3, τ_4, τ_5. τ_0, τ_1, τ_2 and τ_3 are given in TABLE. 4.6. The values τ_4 and τ_5 are got by examining the differences $\tau_1 - \tau_0 = 3.5$, $\tau_3 - \tau_2 = 3$ and $\tau_2 - \tau_1 = 9$. We then take the difference between τ_4 and τ_3 as equal to 9 and that between τ_5 and τ_4 as 3.5 and thus we have $\tau_4 = 28.5$ and $\tau_5 = 32$.
FIG. 4.7.4 shows the simulated time dependent mosquito births.

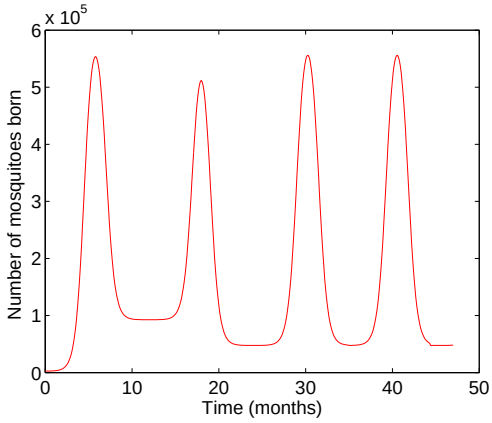


FIG. 4.7. Mosquito births

Infection term

This is calculated from two terms, the probability of transmission of malaria from mosquito to human, p_{vh} or the probability of transmission of malaria from human to mosquito, p_{hv} and the mosquito biting rate.
p_{vh} ranges from 0.01 to 0.2 [17] and p_{hv} ranges from 0.2 to 0.5 [58, 101, 105, 175]. The mosquito biting rate is given as 0.3 per day [58, 101, 105, 175].
We estimated these probabilities of transmission of malaria for the different age groups and

their values are given in TABLE. 4.6. Furthermore, asymptomatic and symptomatic individuals have differences in infection rates. It is not clear which of the two kinds of individuals is more infectious than the other [103], because some studies report that asymptomatic individuals are more infectious than symptomatic individuals [4, 156] and others report the opposite [67]. However, for our model simulations, we considered that the infection rate of asymptomatic individuals is reduced by a factor $\zeta_m = 0.5$ as compared to symptomatic individuals.

Rate into emergency and reactivation rate

The rate of progressing to severe disease depends on the time taken before one becomes an emergency case. It may differ in different individuals depending on their immunity to the disease. Individuals who have not been exposed to malaria before may develop severe disease in 3 to 30 days after infection if not treated, yet it might take 14 days even months for those who have been exposed to malaria [189]. The rates out of emergency for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ were estimated and their values are in TABLE. 4.6.

Individuals with malaria infection may develop symptomatic malaria after infection or they may stay with the infection and reactivate it later. In [189], it may take months and even years before malaria infection is reactivated and it might be due to the individuals immunity being compromised by other infections. We estimated the reactivation rates for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ and their values are given in TABLE. 4.6.

Malaria death rates

One of our model's assumption is that deaths due to malaria occur only in the severe class and that individuals with symptomatic malaria just experience natural death as the susceptible individuals (fully susceptible and asymptomatic individuals).
For individuals who are untreated, the average duration that they spend in the severe disease class is unknown as there is very little literature on severe disease in untreated individuals and an experiment carried out to that effect would be unethical. In [189], it is said that death from severe disease may occur within hours or days. Lubell et al [111] state that the probability of dying from severe malaria in untreated cases is 73% for low

transmission settings and it is 60% for high to medium transmission settings. However, there is no time frame mentioned. Thus, we use the population mortality rates of all malaria that are given in [2, 117, 127, 178, 206] and choose the severe malaria induced death rates such that they show these population mortality rates. Please note that the death rate experienced by individuals with severe malaria will be a summation of the natural death rate and the severe malaria induced death rate. These death rates are given in TABLE. 4.4.

Prevalence of malaria parasitaemia

This ranges from 15% to 81% [138, 149, 152] in children less than 10 years of age depending on the area. In individuals greater than 5 years of age, it was given as 24.7% in very high transmission districts and 16.8% in moderate to high transmission districts [138]. It is measured by either microscopy, RDTs or PCR. Microscopy and RDTs are the most commonly used though the most sensitive method is PCR [27, 150].

4.7.5 Parameters of pneumonia

Infection rate

This is the rate at which individuals acquire pneumonia infection. In [176], the probability of acquisition of different serotypes of *S. pneumoniae* in young children ranged from 0.00007 to 0.0059 per day which gives a range of rates from 0.025 to 2.16 per year.
Only a proportion of individuals with pneumonia infection develop symptomatic pneumonia and it is dependent on the age and immune status of the individual. Moreover, asymptomatic individuals are less infectious than symptomatic individuals, their infectiousness is reduced by a factor $\zeta_p = 0.5$.

Rate into emergency and reactivation rate

Severe disease occurs mostly in children under five years of age. Children may develop severe pneumonia in the range of 3 to 7 days [98]. Severe disease does occur in adults but rarely and there might be other underlying causes such as infection with malaria.

TABLE. 4.4. Demography parameters and parameters of malaria

Parameter	Description	Value (unit time)	Reference
ρ	Human birth rate	0.0435 (yr^{-1})	Chosen [85, 148, 149]
$\mu_c,\ \mu_b,\ \mu_a$	Natural death rates	0.026, 0.004, 0.008 (yr^{-1})	Spectrum [87]
$\eta_1,\ \eta_2,\ \eta_3$	Aging rates	0.19, 0.13, 0.057 (yr^{-1})	Chosen
a_b	Number of bites per mosquito per unit of time	0.3 (day^{-1})	[58, 101, 105, 175]
ζ_m	Reduction in infectiousness of asymptomatic individuals	0.5	Chosen [4, 156]
μ_v	Death rate of mosquito	0.1 (day^{-1})	[58, 101, 105, 175]
$\mu_{\widetilde{M_c}},\ \mu_{\widetilde{M_b}},\ \mu_{\widetilde{M_a}}.$	Death rate in emergency	0.028, 0.109, 0.0107 (mth^{-1})	Chosen
$m_c,\ m_b,\ m_a$	Proportion with asymptomatic malaria	0.5, 0.3, 0.2	[118, 149]
$m_{1c} = m_{2c},\ m_{1b} = m_{2c},\ m_{1a} = m_{2a}$	Proportion of new infections and reinfections that develop symptomatic disease	0.1, 0.05, 0.05	Assumed

Some individuals with asymptomatic pneumonia may reactivate their infection.

The rates into emergency and the reactivation rates for individuals in the three age groups were estimated and their values are given in TABLE 4.6.

Death rates

As with the malaria, we consider that only individuals with severe pneumonia die due to pneumonia. Lubella et al [111] state that the probability of dying from a severe illness requiring antibiotics ranges from 28% to 68%. On the other hand, the case fatality ratio of

non-severe pneumonia ranges from 3% to 10% and that of severe pneumonia ranges from 10% to 50%[13, 18, 55, 57, 60, 98, 102, 128, 166, 177, 179, 182]. However, we are unable to use this information because the time frame for untreated individuals with pneumonia is unknown.

In [161], pneumonia induced mortality rate for children less than 5 years of age was given as 67.5 per $10,000$. For the other age groups, it is less than 5 per 1000 [2].
Thus, we choose the death rate for severe pneumonia so as to reflect these population mortality rates. The death rates for individuals with severe pneumonia for the three age groups is given in TABLE 4.5.

TABLE. 4.5. Parameters of pneumonia model

Parameter	Description	Value (unit time)	Reference
β_{P_c}, β_{P_b}, β_{P_a}	infection rates	0.025 to 4.38 (yr^{-1})	[3, 176, 187]
ζ_p	Reduction in infectiousness of asymptomatic individuals	0.5	Chosen
$\mu_{\widetilde{P_c}}$, $\mu_{\widetilde{P_b}}$, $\mu_{\widetilde{P_a}}$	Pneumonia death rate in emergency	0.302, 0.759, 0.117 (mth^{-1})	
p_c, p_b, p_a	proportion with asymptomatic pneumonia	0.6, 0.3, 0.2	[22, 91]
$p_{1c} = p_{2c}$, $p_{1b} = p_{2b}$, $p_{1a} = p_{2a}$	Proportion of new infections and reinfections that develop symptomatic disease	0.15, 0.05, 0.01	[69]

4.7.6 Parameters of malaria-pneumonia coinfection

Proportion of coinfection

The proportion of individuals with malaria who have pneumonia ranges from 4% to 37% [16, 19, 20, 54, 99, 173]. However, it is important to note that some studies such as the one by Karin et al. [99] were presumptive and most of the studies were carried out among children of less than 5 years of age.

The proportion of children with ARIs (pneumonia) who had malaria was 45% in [60].

Death rates

The death rate is higher for individuals with malaria-pneumonia coinfection than for individuals with malaria only.
In [16], the case fatality ratio of severe malaria cases who also had bacteraemia was 22.0% yet that of severe malaria cases only was 4% and in [173], the case fatality for children with severe pneumonia and clinical malaria was 14% and that for clinical malaria only was 9%.

There is a 2 to 5 fold increase in mortality if there is bacteraemia (pneumonia) present in children with severe malaria [16, 20, 173]. In our model simulations, we use a 3 fold increase in mortality individuals with severe malaria-pneumonia coinfection.

4.8 Model fitting and parameter estimation

4.8.1 Human and mosquito population

We use a human population of 36000 for the average study site in Arm A and this number is divided into the respective classes of susceptibles, malaria, pneumonia and coinfection.

The population for the mosquitoes is determined by using the Entomological Inoculation Rate (EIR) which is expressed in terms of average numbers of infective bites per person per unit time. It is simply the product of the human biting rate and prevalence of sporozoites in the mosquito population [17, 76, 93, 97] which gives the number of infective bites per person per unit time.
In equation terms and in relation to our model, the EIR is given as $a_b \frac{I_v}{N_v} \frac{N_v}{N}$, where a_b is the mosquito biting rate given per year. $\frac{I_v}{N_v}$ is the sporozoite rate and $\frac{N_v}{N}$ is the mosquito to human ratio.

In Uganda, about 70% of the regions have an EIR > 100 and about 20% have an EIR > 10 and the other 10% have an EIR > 1% [152, 206]. The sporozoite rate ranges from 1% to 20% [17, 50, 53, 97, 106].

We use an EIR of approximately 130 per year and a sporozoite rate of 19% to give a ratio of mosquito to humans. Multiplying this ratio with the human population gives us the population of mosquitoes at the site of 224946.
Note that the sporozoite rate of 19% is the fitted value that we get and it is the average considering all the available months of data. However, we use a sporozoite rate of 5% for initial conditions so as to capture the low malaria values at baseline.
Our initial conditions for the model are:

$$S_c(0) = 6605,\ P_c(0) = 20,\ M_c(0) = 109,\ PM_c(0) = 6,\ \widetilde{PM_c}(0) = 100$$

$$S_b(0) = 9604,\ P_b(0) = 6,\ M_b(0) = 78,\ PM_b(0) = 0,\ \widetilde{PM_b}(0) = 32$$

$$S_a(0) = 19251,\ P_a(0) = 28,\ M_a(0) = 111,\ PM_a(0) = 1,\ \widetilde{PM_a}(0) = 49$$

$$S_v(0) = 213699,\ I_v(0) = 11247.$$

4.8.2 Fitting baseline data

We fit baseline data from Arm A sites using an optimization tool built in Matlab that uses the least squares method and goodness of fit techniques. The data fitted are the average predicted number of malaria cases and the average predicted number of pneumonia cases for an average study site of Arm A.
The number of pneumonia cases at baseline for the three age groups, $[0, 5)$, $[5, 14)$ and $[14, 50)$ are given in TABLE. 3.2.
FIG. 3.1(a), FIG. 3.1(b) and FIG. 3.1(c) show the predicted number of malaria cases for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ at baseline and after the two interventions of Integrated Management of Infectious Disease (IMID) training and On-Site Support Services (OSS).

Malaria data is seasonal with a peak in the June of the first year and July of the second year and these months correspond to the rainy season in Uganda.
To capture this dynamics, we use a time dependent mosquito birth rate (refer to subsection 4.7.4) since it is known that the number of mosquitoes increases during the rainy season due to the availability of stagnant pools of water for breeding of mosquitoes.
Individuals in the population have asymptomatic malaria infection and thus high numbers of mosquitoes lead to an increase in malaria transmission which in turn translates into

disease and explains the peak in the number of malaria cases that is seen at health facilities [29, 47, 65] during the rainy season.

TABLE. 4.6 gives the fitted parameter values for the baseline data. The rates' units are in months.
The model fits to the malaria data using the optimization tool built in Matlab are given in FIG. 4.8(a), FIG. 4.8(b) and FIG. 4.8(c).
FIG. 4.9(a) is the fit to pneumonia data and FIG. 4.9(b) of malaria-pneumonia cases is a consequence of the first two fits.

TABLE. 4.6. Estimated parameters with baseline data

Parameter	Estimated value
$b_0,\ b_1,\ b_2,\ b_3$	2567, 649900, 125232, 649900
$\tau_0,\ \tau_1,\ \tau_2,\ \tau_3$	4.0, 7.5, 16.5, 19.5
k	0.9
$\alpha_{P_c} = \alpha_{PM_c},\ \alpha_{P_b} = \alpha_{PM_b},\ \alpha_{P_a} = \alpha_{PM_a}$	2.0278, 0.1521, 0.1217
$\alpha_{M_c},\ \alpha_{M_b},\ \alpha_{M_a}$	0.468, 0.1014, 0.1014
$\beta_{P_c},\ \beta_{P_b},\ \beta_{P_a}$	0.0353, 0.0128, 0.0238
$\omega_{P_c},\ \omega_{P_b},\ \omega_{P_a}$	0.0459, 0.0075, 0.0295
$\vartheta_{P_c},\ \vartheta_{P_b},\ \vartheta_{P_a}$	0.04, 0.0317, 0.0408
$p_{vhc},\ p_{vhb},\ p_{vha}$	0.025, 0.045, 0.02
$p_{hvc},\ p_{hvb},\ p_{hva}$	0.015, 0.305, 0.89
Duration of symptomatic malaria and coinfection disease	7 days
Duration of symptomatic pneumonia	3 days

At baseline, the prevalence of severe cases for malaria-pneumonia coinfection is 7%, pneumonia is 2% and that of malaria is 25%. The incidence rate of malaria disease is 0.03 per month for $[0, 5)$ age group, 0.02 per month for $[5, 14$ and 0.015 per month for the $[14, 50)$ age group as shown in FIG. 4.14(c).
The incidence rate of pneumonia disease is 0.03 per month for $[0, 5)$ age group, 0.02 per month for $[5, 14$ and 0.015 per month for the $[14, 50)$ age group as shown in FIG. 4.19(c).

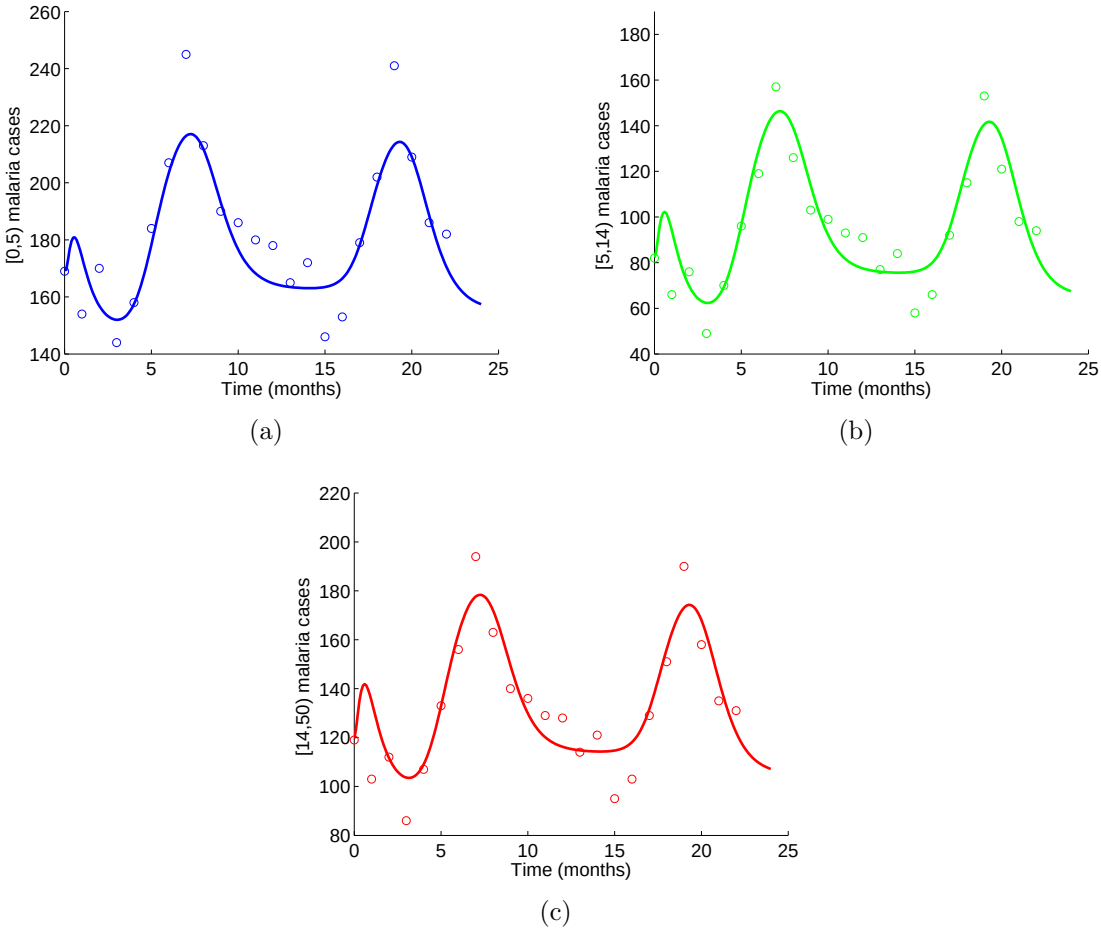
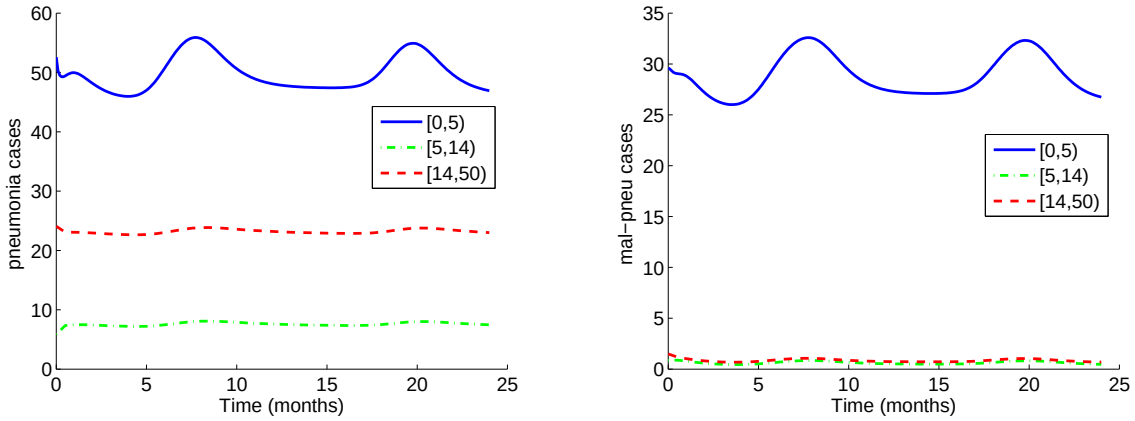


FIG. 4.8. Fitting malaria cases at baseline for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$

4.8.3 Fitting intervention data

In fitting IMID combined with OSS data, we change the parameters of recovery rate and the rate out of emergency according to the changes in the indicators after the intervention. We make use of the following formula:

$$\begin{aligned}\text{Indicator after intervention} \;=\; &\text{indicator before intervention} \times (1 + (\text{coverage of intervention} \\ &\times \text{impact of intervention on indicator}))\end{aligned}$$



(a) (b)

FIG. 4.9. Pneumonia and coinfection cases for baseline for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$. The number of $[0, 5)$ coinfection cases per month is about 30 and it is about 2 cases each for $[5, 14)$ and $[14, 50)$

Coverage of intervention

This was expressed as the percentage of patients that were attended to by MLPs who had taken part in IMID training (IMID intervention) and those that had attended OSS (OSS intervention).

The coverage of intervention with IMID was calculated using IDCAP data on the percentage of patients who were attended to by clinicians who had taken part in IMID training. It was given as 26% across all age groups.

For the combination intervention of IMID and OSS, we used the coverage of intervention as 21% for the $[0, 5)$ and 60% for the $[5, 14)$ age groups and 40% for the $[14, 50)$ age group for the model to fit the data. Please note that in this case, we did not make use of an optimization tool because the only value that was needed for the fit was the coverage of the intervention and we could easily vary it until we obtained a reasonable fit.

To estimate the effect of IMID only as well as the incremental effect of OSS, we used the impact of IMID and IMID+OSS on the indicators as calculated in section 3.3 and given in TABLE. 3.4.

4.9 Numerical results

4.9.1 Malaria

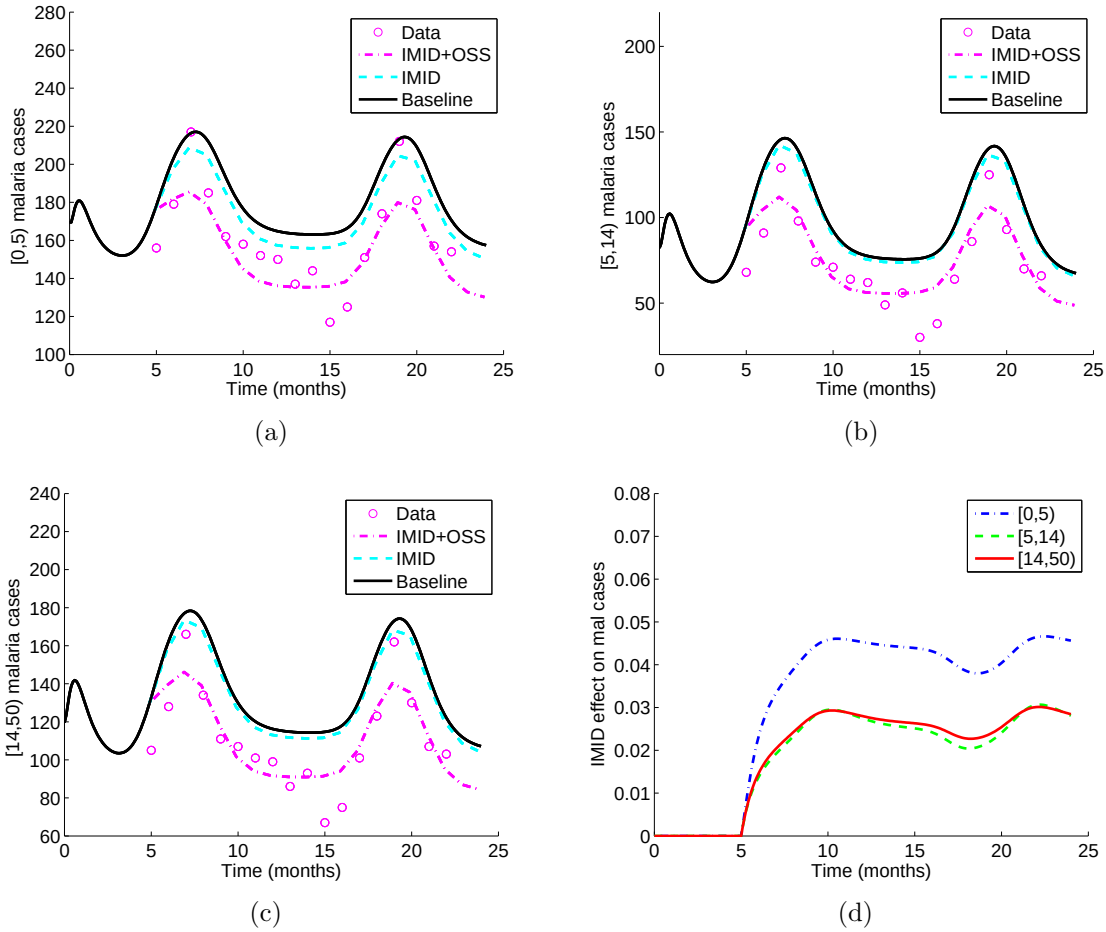
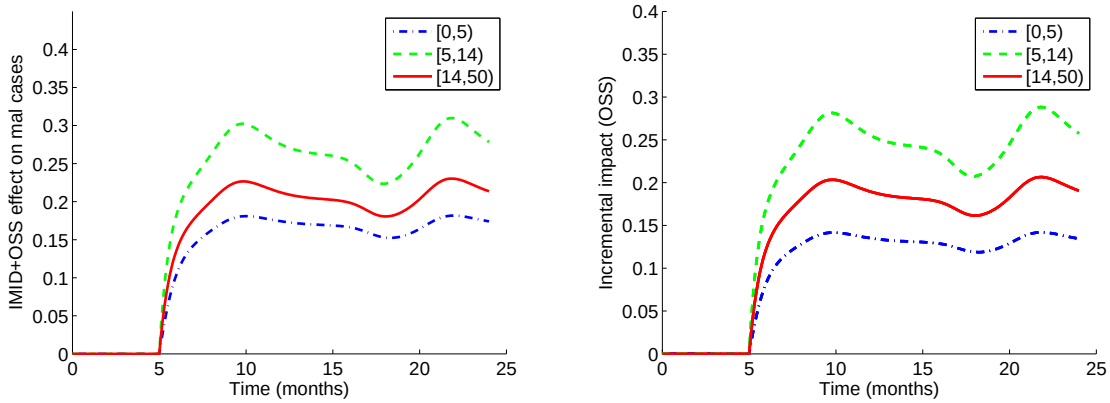


FIG. 4.10. Model fit to malaria cases after combination intervention of IMID and OSS for age groups $[0,5)$, $[5,14)$ and $[14,50)$ in FIG. 4.10(a), FIG. 4.10(b), FIG. 4.10(c). The effect of IMID, IMID+OSS and incremental impact of OSS on all malaria cases is shown in FIG. 4.10(d).

FIG. 4.10(a), FIG. 4.10(b) and FIG. 4.10(c) show a decrease in the number of malaria cases after the intervention of IMID and the IMID+OSS intervention for the $[0,5)$, $[5,14)$ and $[14,50)$ age groups respectively.

The effect of IMID increases initially for a period of five months of the IMID intervention and then stays relatively constant for the rest of the intervention as displayed by FIG.

4.10(d). After the initial increase during the first five months of the IMID intervention, the effect of IMID for the $[0, 5)$ age group remains constant with an average value of 4.4% for the rest of the intervention period. For the $[5, 14)$ age group, the average effect of IMID after the initial rise in the first five months is 2.6%. For the $[14, 50)$, the effect of IMID increases for a period of five months and then stays constant with an average effect of 2.7% for the rest of the intervention period.



(a) (b)

FIG. 4.11. Effect of OSS on malaria cases for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ in FIG. 4.11(a), FIG. 4.11(b), gives the incremental impact of OSS on malaria cases for the three age groups.

There is a noted initial rise in the effect of IMID+OSS intervention and the incremental impact of OSS on malaria cases for the first five months after the start of the intervention across all age groups and then it stabilizes as displayed in FIG. 4.11(a). The average effect of OSS on malaria cases for the $[0, 5)$ age group is 17%, 26.9% for the $[5, 14)$ age group and 20.7% for the $[14, 50)$ for the remaining intervention period.

FIG. 4.11(b) shows the incremental impact of OSS across all the three age groups. There is a rise in the incremental impact of OSS for the first five months of the intervention and then it stabilizes for the remaining period of the intervention. The average incremental impact of on malaria cases for the stable period is 13.2%, 24.9%, 18.6% for the $[0, 5)$, $[5, 14)$, $[14, 50)$ age groups respectively.

There is a decline in the number of malaria deaths across all age groups as displayed in FIG. 4.12(a), FIG. 4.12(b) and FIG. 4.12(c). The average effect of IMID on malaria deaths

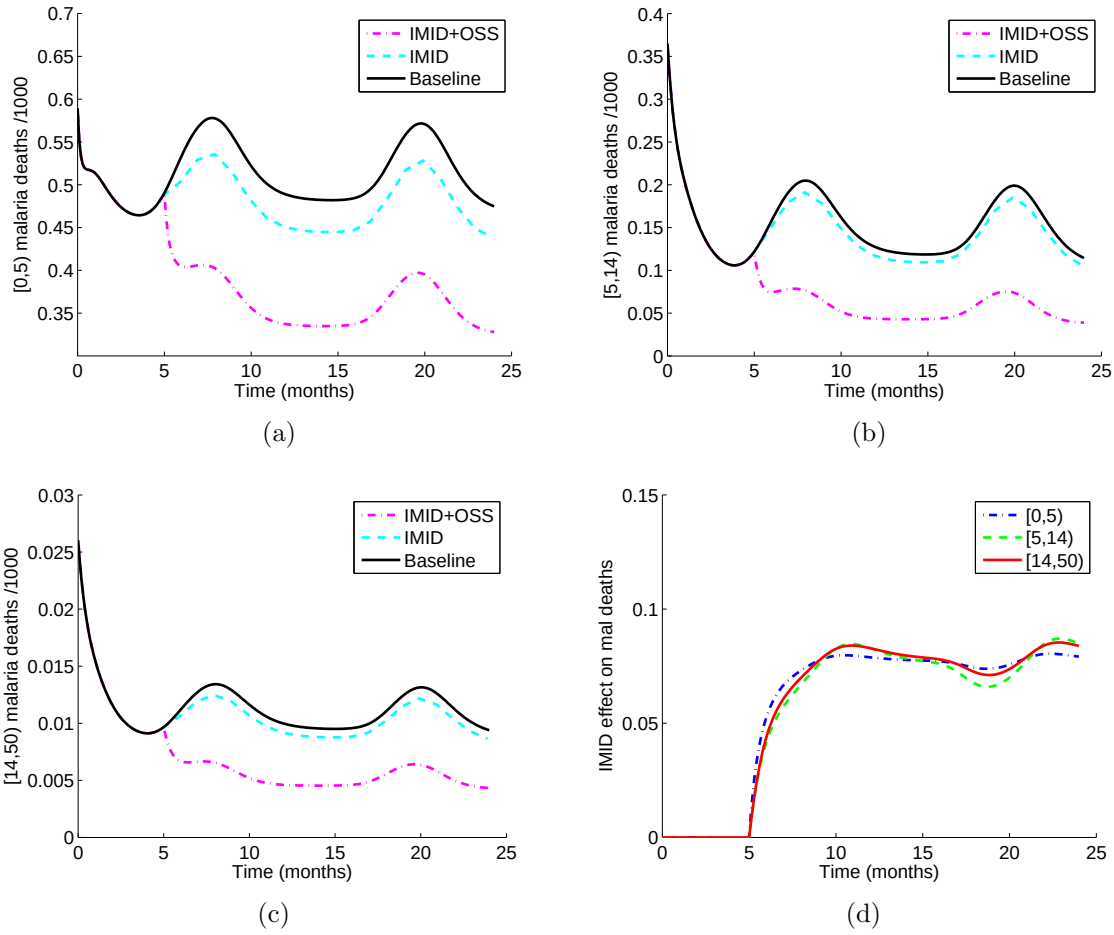
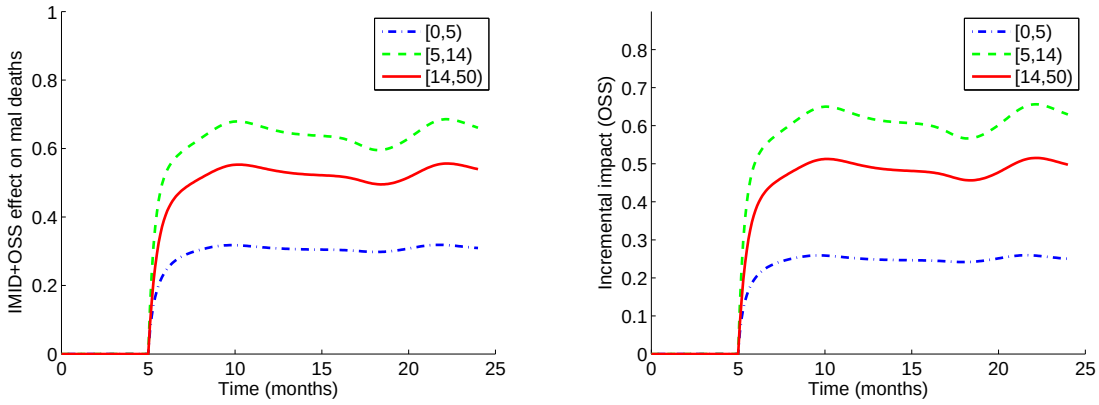


FIG. 4.12. Malaria deaths for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ in FIG. 4.12(a), FIG. 4.12(b), FIG. 4.12(c) respectively. FIG. 4.12(d) illustrates the effect of IMID, IMID+OSS and incremental impact of OSS on all malaria deaths

is a decrease of approximately 7.8% for all the age groups as shown in FIG. 4.12(d).

The average effect of IMID+OSS on malaria deaths for the remaining intervention period after the initial rise in the first five months is a fall of 30.8% for the $[0, 5)$ age group, 64.5% for the $[5, 14)$ age group and 52.9% for the $[14, 50)$.

The incremental impact of OSS also rises in the initial five months and then relatively stabilizes for the rest of the intervention period. For the $[0, 5)$ age group, the incremental impact of OSS is a decline of 25% and it is 61.5% and 48.8% for the $[5, 14)$ and $[14, 50)$ respectively.



(a) (b)

FIG. 4.13. Effect of OSS on malaria deaths in FIG. 4.13(a) and the incremental impact of OSS on malaria cases for the three age groups in FIG. 4.13(b).

In FIG. 4.14(a),malaria disease prevalence decreases with the interventions of IMID and combination intervention of IMID and OSS from a baseline value of 1.41% to 1.2% with the combination intervention of IMID and OSS.

The effect of IMID on all malaria disease prevalence is a decrease of 3.2%. The effect of OSS is a decline of 19.7% and the incremental impact of OSS is 17.1%. This is displayed in FIG. 4.14(b).

In FIG. 4.14(c), there is no change in malaria incidence with the intervention across all age groups.

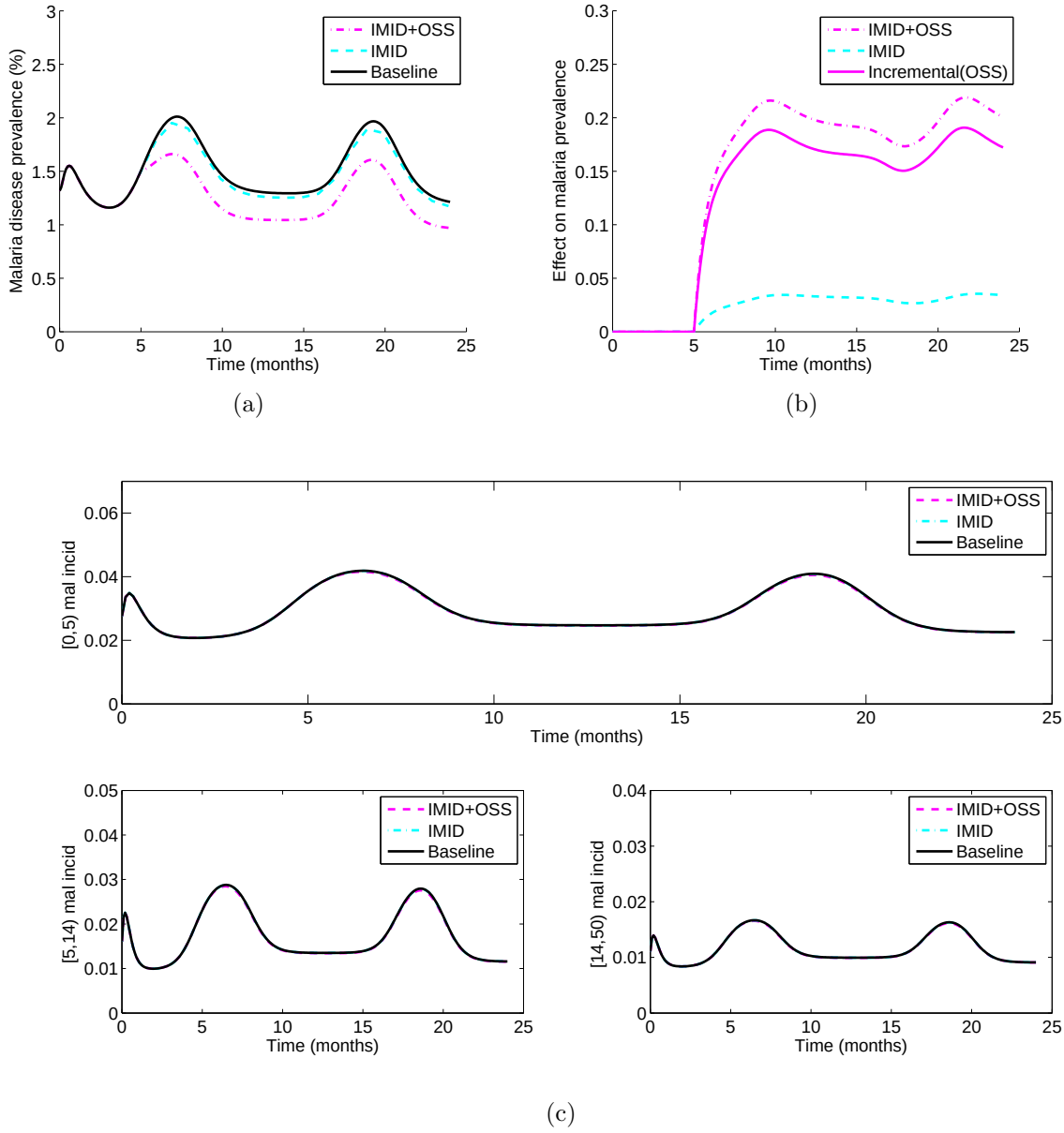


FIG. 4.14. Malaria disease prevalence for all individuals in FIG. 4.14(a) and the effect on malaria prevalence in FIG. 4.14(b). FIG. 4.14(c) shows the malaria incidence for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups

4.9.2 Pneumonia

FIG. 4.15(a), FIG. 4.15(b) and FIG. 4.15(c) show a decrease in the number of pneumonia cases after the interventions for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively. How-

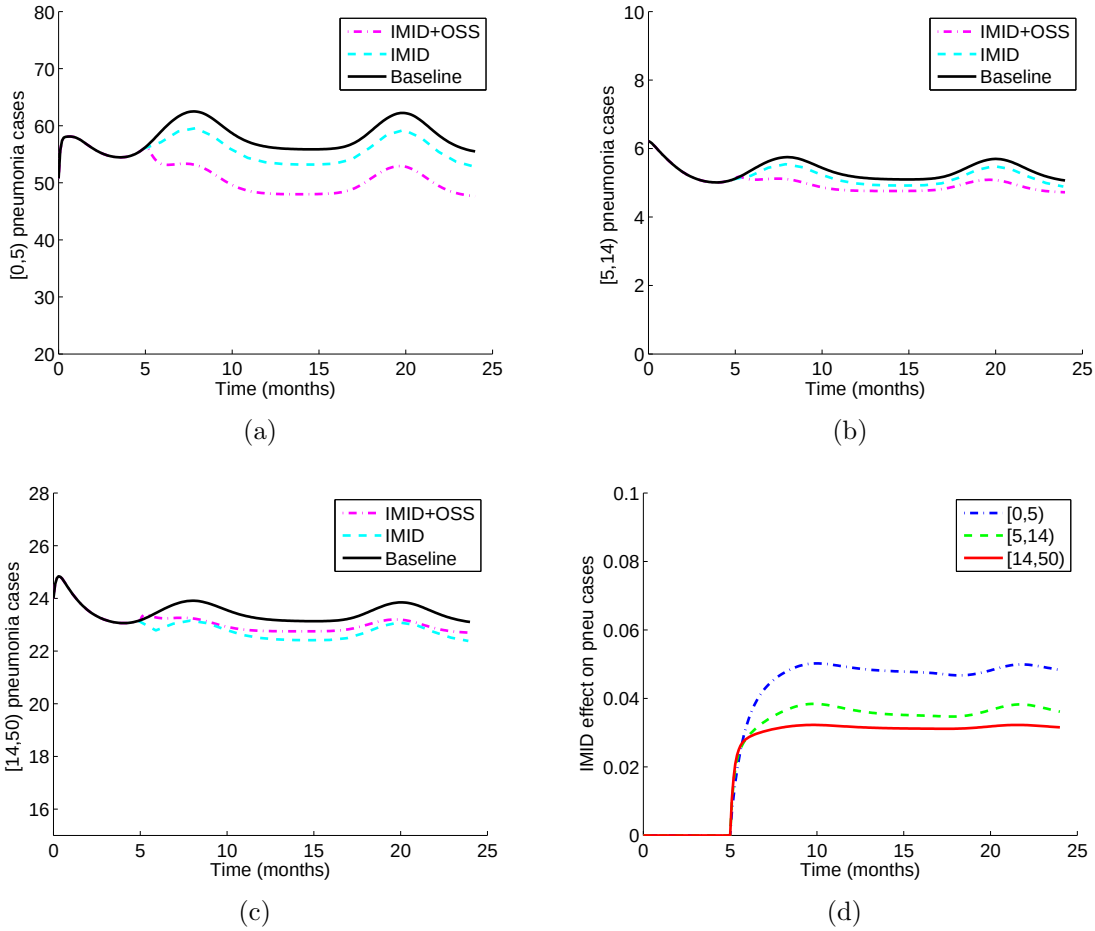
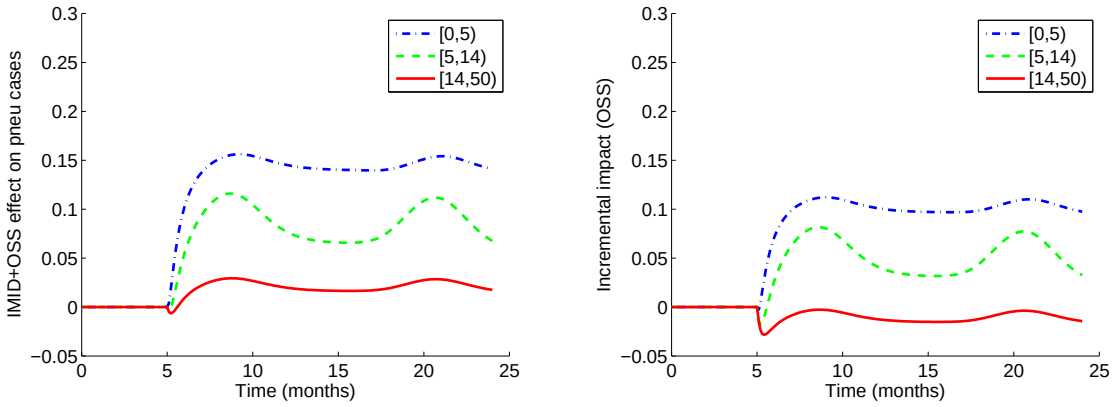


FIG. 4.15. Pneumonia cases for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ in FIG. 4.15(a), FIG. 4.15(b), FIG. 4.15(c). The effect of IMID and OSS, IMID and the incremental impact of OSS is shown in FIG. 4.15(d).

ever, for the $[14, 50)$ age group, the IMID intervention reduces the number of pneumonia cases than the combination intervention of IMID and OSS.

The effect of IMID increases initially for a period of five months of the IMID intervention and then stays relatively constant for the rest of the intervention as displayed by FIG. 4.15(d). The effect of IMID for the $[0, 5)$ age group for the rest of the intervention after the initial rise in the first five months is on average a decrease of 4.8%. For the $[5, 14)$ and $[14, 50)$ age groups, it is 3.6% and 3.2% respectively.

There is a noted initial rise in the effect of IMID+OSS and the incremental impact of OSS on pneumonia cases for the first five months after the start of the intervention across



(a) (b)

FIG. 4.16. The effect of combination intervention of IMID and OSS and the incremental impact of OSS in FIG. 4.16(a) and 4.16(b)

all age groups and then it stabilizes as displayed in FIG. 4.16(a). The average effect of IMID+OSS on pneumonia cases for the $[0, 5)$ age group is 14.6%, 8.3% for the $[5, 14)$ age group and 2.1% for the $[14, 50)$ for the remaining intervention period.

FIG. 4.16(b) shows the incremental impact of OSS across all the three age groups. For the $[0, 5)$ and $[5, 14)$ age groups, the incremental impact of OSS is positive which implies that there is an additional benefit in having the OSS intervention. However, this is not the case for the $[14, 50)$ age group where the incremental impact of OSS is negative meaning that the OSS intervention is not needed for this age group infact it does not do well. The average incremental impact of on pneumonia cases for the stable period after the first five months is 10.2%, 4.9%, -1.1% for the $[0, 5)$, $[5, 14)$, $[14, 50)$ age groups respectively.

There is a decline in the number of pneumonia deaths across all age groups as displayed in FIG. 4.17(a), FIG. 4.17(b) and FIG. 4.17(c). The average effect of IMID on pneumonia deaths is a decrease of approximately 7.8% for all the age groups as shown in FIG. 4.17(d).

The average effect of IMID+OSS on pneumonia deaths for the remaining intervention period after the initial rise in the first five months is a fall of 30.8% for the $[0, 5)$ age group, 64.5% for the $[5, 14)$ age group and 52.9% for the $[14, 50)$.

The incremental impact of OSS also rises in the initial five months and then relatively stabilizes for the rest of the intervention period. For the $[0, 5)$ age group, the incremental

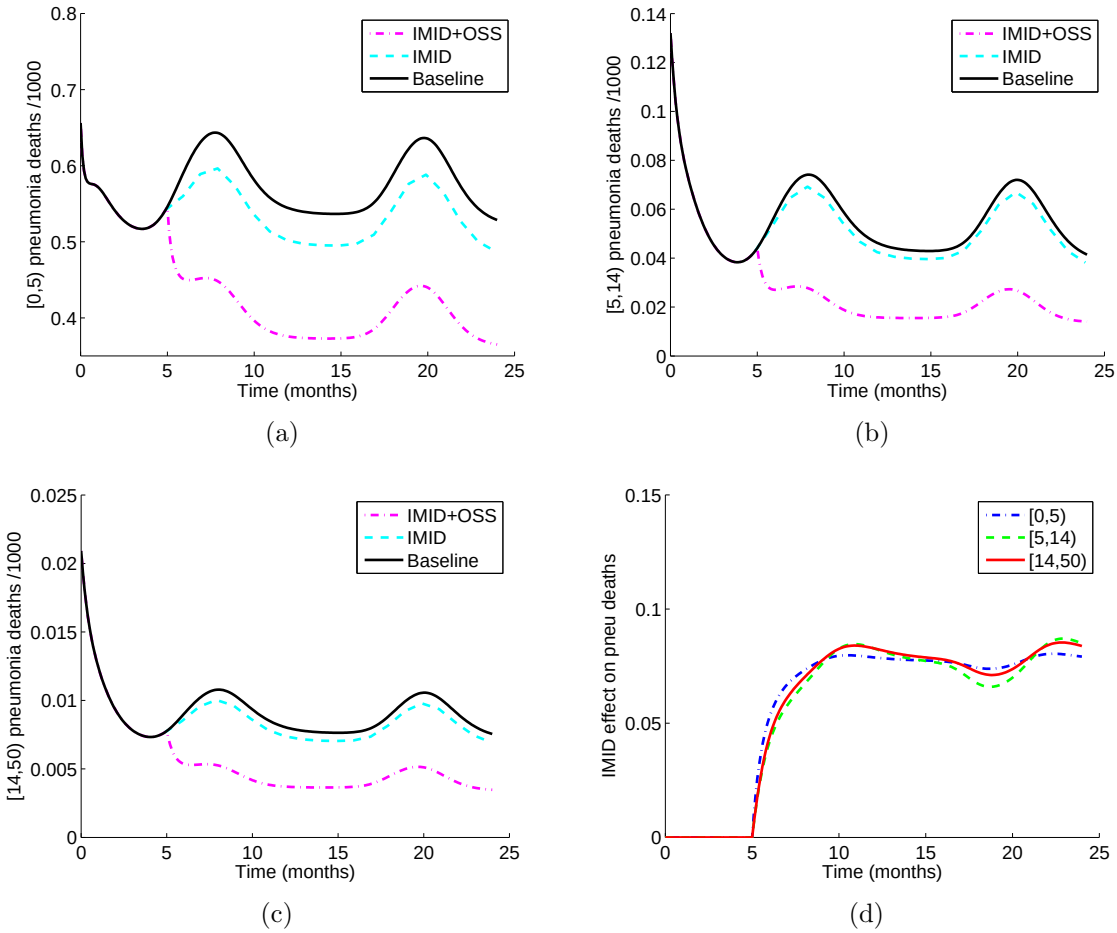


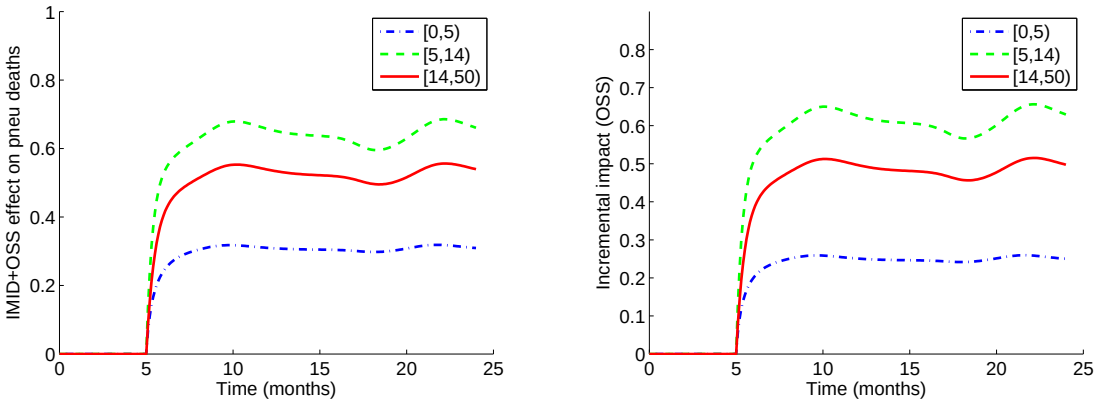
FIG. 4.17. Deaths due to pneumonia for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$. The effect of IMID, and IMID+OSS on pneumonia deaths is displayed in FIG. 4.17(d)

impact of OSS is a decline of 25% and it is 61.5% and 48.8% for the $[5, 14)$ and $[14, 50)$ respectively.

In FIG. 4.19(a),pneumonia disease prevalence decreases with the interventions of IMID and combination intervention of IMID and OSS from a baseline value of 31.3% to 29.1% with the combination intervention of IMID and OSS.

The effect of IMID on all pneumonia disease prevalence is a decrease of 4.1%. The effect of IMID+OSS is a decline of 9.2% and the incremental impact of OSS is 5.3%. This is displayed in FIG. 4.19(b).

In FIG. 4.19(c), there is no change in pneumonia incidence with the intervention across all



(a) (b)

FIG. 4.18. The effect of IMID+OSS, and incremental impact of OSS on pneumonia deaths is displayed in FIG. 4.18(a) and FIG. 4.18(b)

age groups.

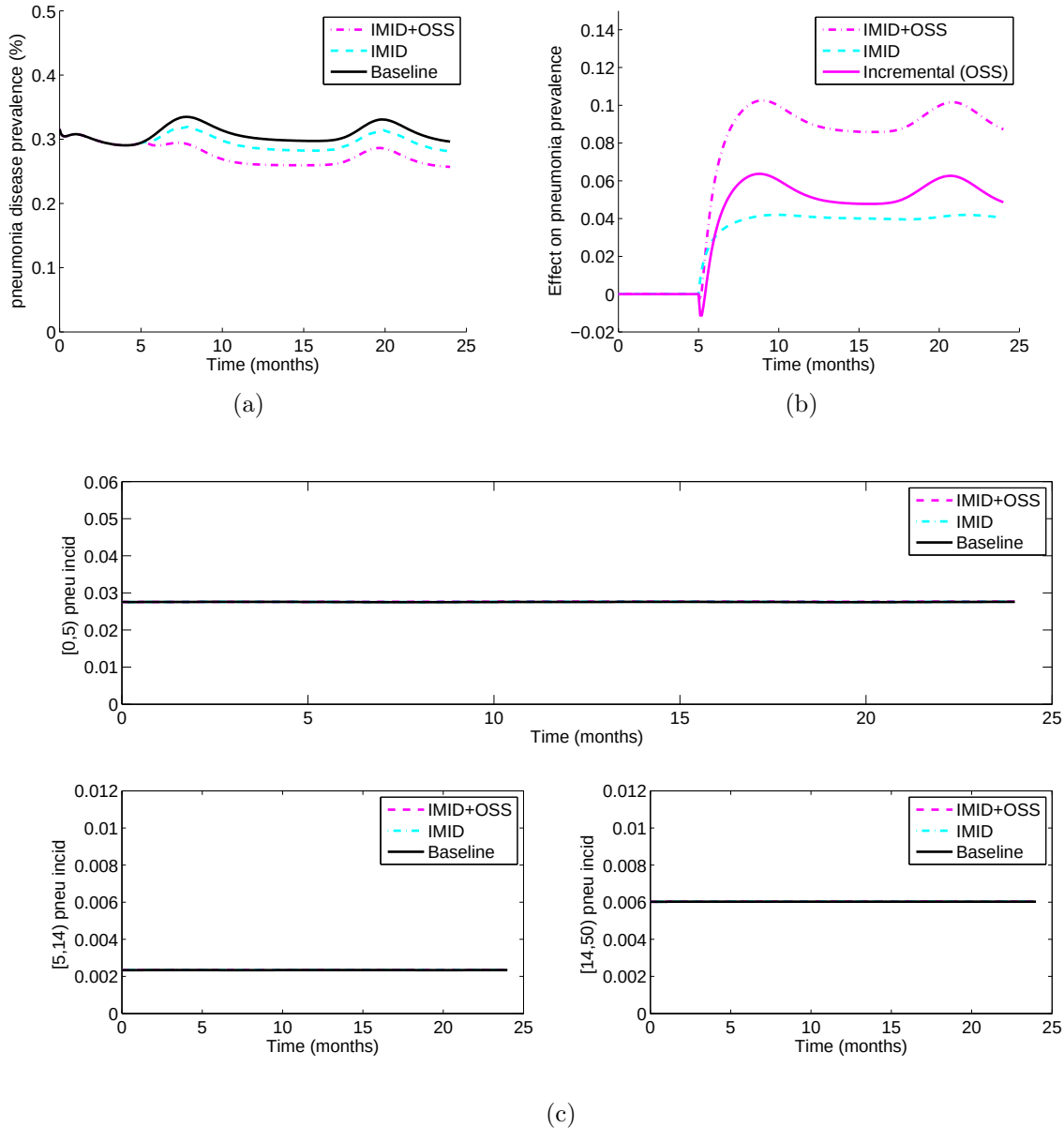


FIG. 4.19. Pneumonia disease prevalence for all age groups in FIG. 4.19(a) and the effect on prevalence in FIG. 4.19(b), FIG. 4.19(c) illustrates the pneumonia incidence for age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$.

4.9.3 Malaria-pneumonia coinfection

In FIG. 4.20(a), the prevalence of coinfection disease declines by both interventions. The effect on coinfection prevalence is a reduction of 6.5% by IMID and 24% by IMID and OSS

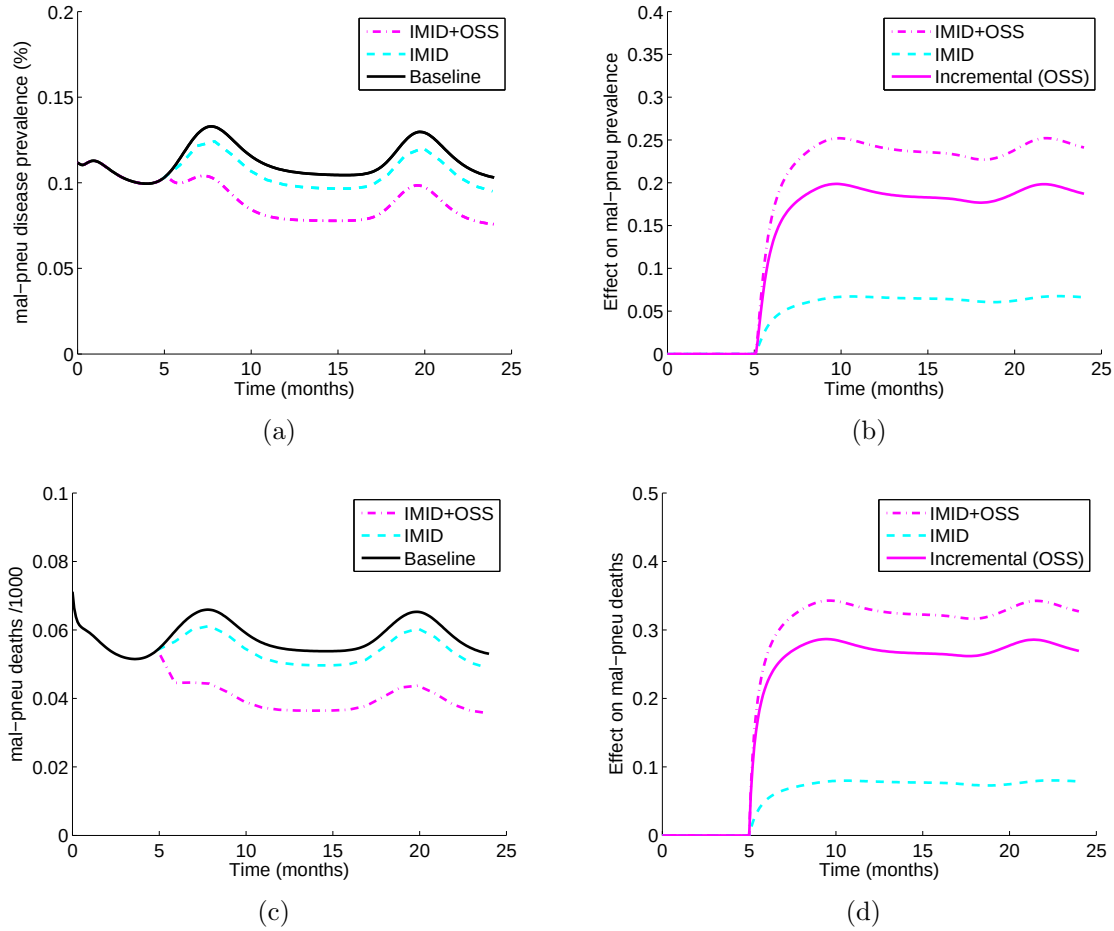


FIG. 4.20. Malaria-pneumonia disease prevalence for all age groups in FIG. 4.20(a) and the effect on prevalence in FIG. 4.20(b), FIG. 4.20(c) shows the malaria-pneumonia deaths for all age groups and the effect on deaths is shown in FIG. 4.20(d).

together and the incremental impact of OSS is a fall of 18.7% as given in FIG. 4.20(b).

In FIG. 4.20(c), the number of malaria-pneumonia deaths decrease with the interventions. The effect on malaria-pneumonia deaths is a reduction of 7.7% by IMID and 32.9% by IMID and OSS together and the incremental impact of OSS is a reduction by 27.2%.

4.10 Impact by proportion triaged

In this section, we investigate the effect of IMID and IMID+OSS contributed by triaging of patients.

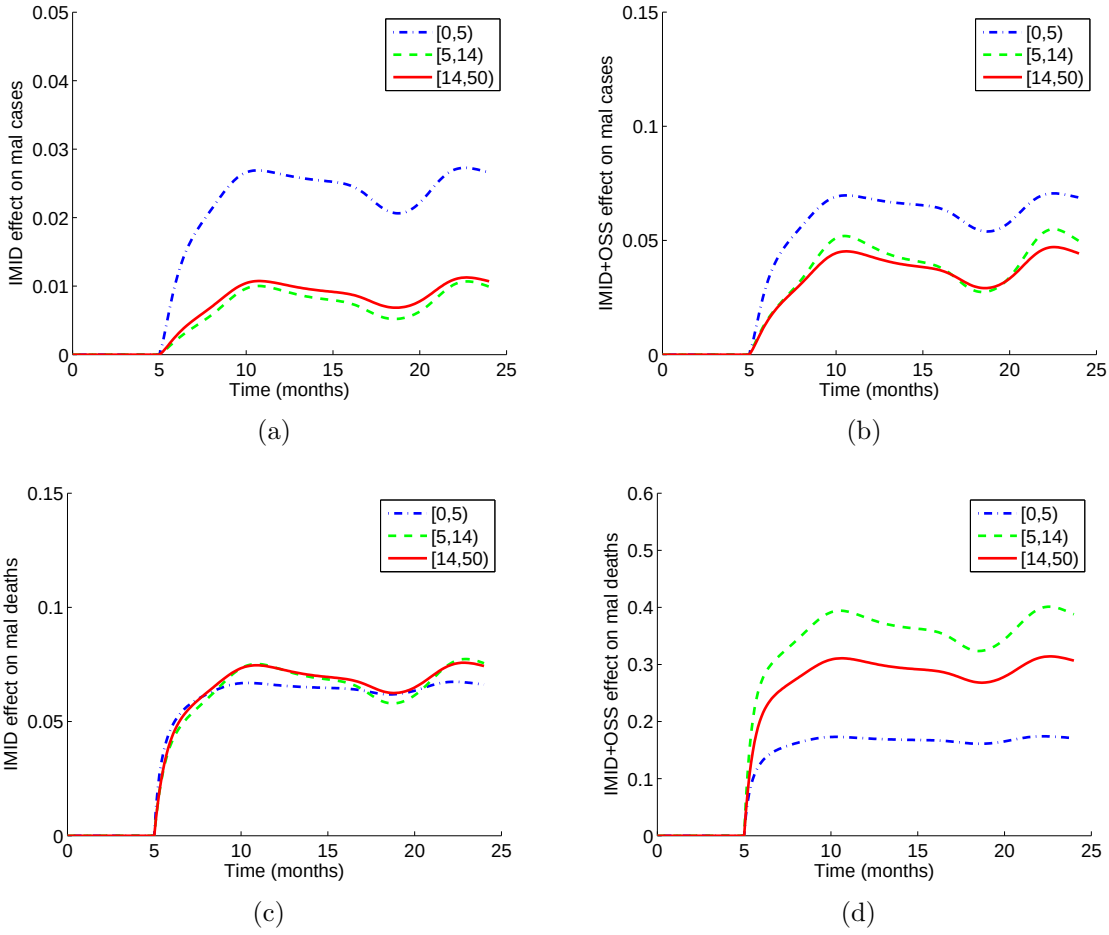


FIG. 4.21. Effect of IMID and IMID+OSS on malaria cases and deaths in FIG. 4.21(a), FIG. 4.21(b), FIG. 4.21(c), FIG. 4.21(d), contributed by proportion triaged

In FIG. 4.21(a), the effect of IMID on malaria cases is 2.5%, 0.82% and 0.93% for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively. The contribution by proportion triaged on the effect of IMID is 56.8%, 31.5% and 34.4% for the respective age groups of $[0, 5)$, $[5, 14)$ and $[14, 50)$.

The effect of IMID+OSS on malaria cases is 6.5%, 4.2%, 3.9% for the $[0, 5)$, $[5, 14)$ and

$[14, 50)$ age groups accordingly as illustrated in FIG. 4.21(b). The proportion triaged contributes 38.2%, 15.6% and 18.8% to that effect for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ in turn.

In FIG. 4.21(c), the effect of IMID on malaria deaths is 6.5%, 6.9%, 7% for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively. The contribution by proportion triaged on the effect of IMID is 83.3%, 88.5% and 88.6% for the respective age groups of $[0, 5)$, $[5, 14)$ and $[14, 50)$.
The effect of IMID+OSS on malaria deaths is 16.9%, 36.7%, 29.5% for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups accordingly as illustrated in FIG. 4.21(d). The proportion triaged contributes 54.9%, 56.9% and 55.8% to that effect for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ in turn.

In FIG. 4.22(a), the effect of IMID on pneumonia cases is 3%, 1% and 0.45% for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively. The contribution by proportion triaged on the effect of IMID is 62.5%, 27.8% and 14.1% for the respective age groups of $[0, 5)$, $[5, 14)$ and $[14, 50)$.

The effect of IMID+OSS on pneumonia cases is 7.7%, 5.2%, 1.9% for the $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups accordingly as illustrated in FIG. 4.22(b). The proportion triaged contributes 52.7%, 62.7% and 90.5% to that effect for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ in turn.

In FIG. 4.22(c) and FIG. 4.22(d), the effect of IMID and effect of IMID+OSS on pneumonia deaths is the same as that for malaria deaths and also with the same contribution by the proportion triaged on those effects.

4.11 Discussion

We have used a mathematical model to study the coinfection of malaria and pneumonia. The model categorizes individuals according to clinical symptoms with the inclusion of a severe disease class. It is divided into three age groups. We calibrated the model using data on malaria and pneumonia cases collected by IDCAP.

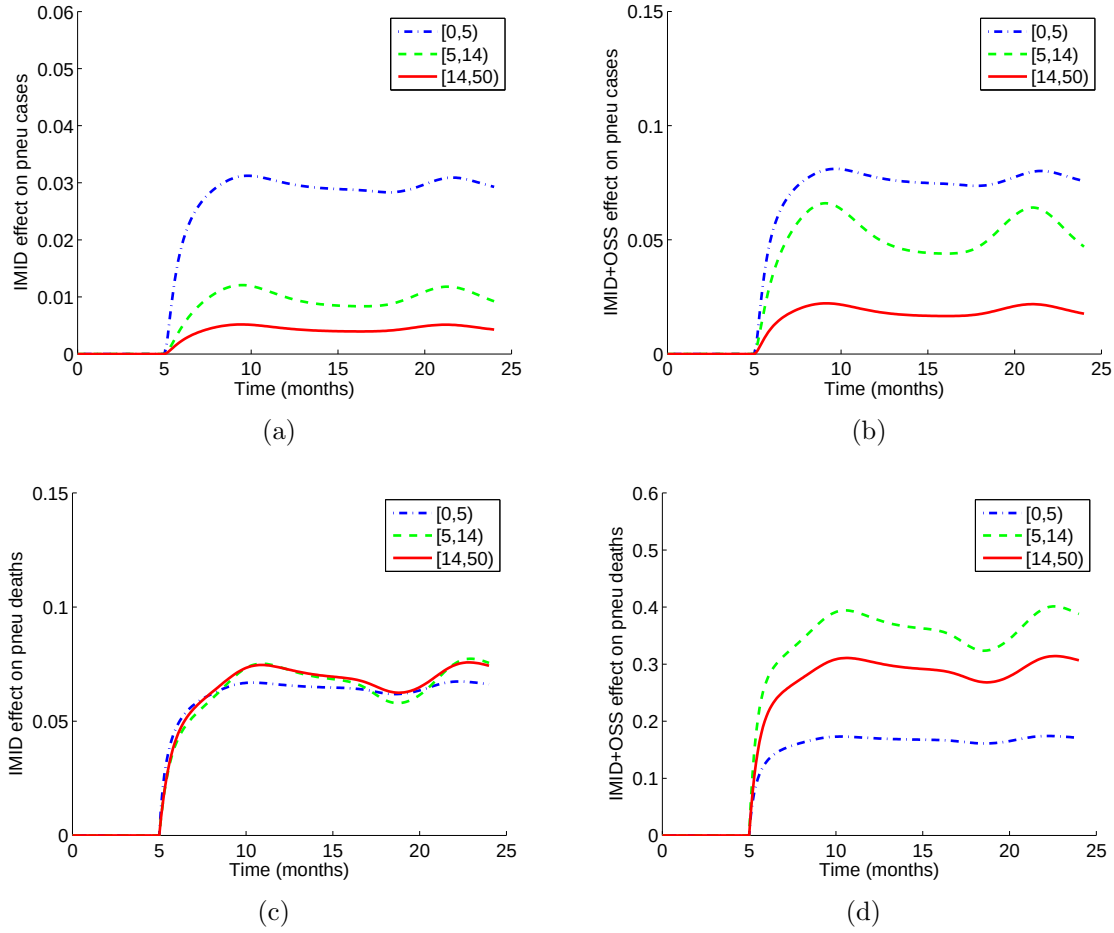


FIG. 4.22. Effect of IMID and IMID+OSS on pneumonia cases and deaths in FIG. 4.22(a), FIG. 4.22(b), FIG. 4.22(c), FIG. 4.22(d), contributed by proportion triaged.

The model was used to investigate the effect of IMID, IMID+OSS and the incremental impact of OSS on number of cases, deaths, prevalence and incidence for malaria and pneumonia, for the period of the intervention. It has been shown that the two training interventions lead to a reduction in the number of cases, deaths and prevalence of disease but not incidence of episodes of disease.

The reduction in the number of disease cases is due to increase in the proportion of patients that receive appropriate medication and the fall in the number of deaths is due to the rise in the proportion of patients triaged. The percentage reduction in the number of deaths for either malaria or pneumonia is the same (7.8%) across all age-groups and for children under 5 years of age, this means that a life is being saved per month.

Considering the incidence of episodes of disease, there is no change in either malaria or pneumonia incidence. This is understandable as IMID and OSS were purely training interventions on case management and not on prevention of infection. Though there is a reduction in number of cases which decreases the infectious reservoir, it is not big enough to result in a decrease in incidence of episodes of disease.

The coverage of the intervention for the combined intervention of IMID and OSS is higher in the $[5, 14)$ age group as compared to the other two age groups and it is lowest in the $[0, 5)$ age group though comparable to that of the $[14, 50)$ age group. The reason for this is that there are more children that come to the clinic as compared to the other age groups and thus the probability that they will be attended to by clinicians trained in IMID+OSS is lower as compared to the other age groups.

The contribution by the proportion triaged to the effect of IMID is more than the contribution to the effect of IMID+OSS for malaria cases while it is the reverse for pneumonia cases. On the other hand, the contribution of proportion triaged to the effect of IMID is more as compared to its contribution to effect of IMID+OSS while considering deaths. Important to note is that the contribution of proportion triaged to the effect of the interventions with regard to deaths is more than 50% which highlights the importance of triaging of patients to prevent deaths.

IMID+OSS and OSS alone perform better than IMID though IMID also has considerable impact. The implication for this is that supervision and practical training are important in case management and that classroom based training is enhanced when a practical component is applied with it.
It is not the first time that the impact of IMID has been investigated. Infact, in [180], the impact of training was shown by the improvement in indicators such as the proportion of patients who were tested and treated. However, this study did not go ahead to investigate what effect improvement of these indicators could have on population outcomes such as prevalence, incidence and mortality.

There are a number of limitations in this study. One of them being that the pneumonia data was lacking and for the most part we relied on the malaria data in estimating coverage

of the IMID+OSS.

It is also important to note that although the IDCAP project considered testing of individuals for malaria and assessment for pneumonia, we were unable to use these results because it was noted that prescription of medication for patients did not depend on testing or assessment results and as such most individuals with fever did receive malaria medication and those that did not get malaria medication were given antibiotics. Besides, most of the individuals who presented with cough and cold were given antibiotics and thus assessment of pneumonia did not matter. In fact some patients were diagnosed with pneumonia even without assessment.

Even with these limitations, the study shows the importance of classroom training as well as the enhanced improvement in population outcomes when practical training is added on.

4.12 Summary

In this chapter, we have explored the transmission dynamics of malaria and pneumonia using models that are relatively simplified. We have carried out a mathematical analysis that looked at the stability analysis of the equilibrium points given by the sub models of malaria and pneumonia. The coinfection model of malaria and pneumonia was extended to include age structure and the different parameters for the model were obtained, some from literature and others from fitting the model to available data.

We then investigated the effect of two training interventions, IMID and IMID with OSS on malaria and pneumonia cases, deaths, prevalence and incidence. The results demonstrated a reduction in number of cases, deaths, prevalence but no change in incidence with the two interventions. Nevertheless, training of MLPs is effective in reducing patient deaths and cases and supervision and practical training does a lot in improving quality of health care.

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Chapter 5

HIV-TB Coinfection

5.1 Introduction

In this chapter, we formulate and use an HIV-TB coinfection model to investigate the effect of IMID and OSS on HIV care and TB management. The reason for this being that individuals infected with HIV progress quickly to active TB disease if they have the TB infection, and also because HIV and TB were part of the infectious diseases that were considered in the IDCAP study.
The points of interest in the management of TB cases were testing, initiation and completion of treatment. For HIV, the areas of concern were: PMTCT, ART enrolment for eligible HIV infected individuals and CTX coverage.

IDCAP evaluated the effect of IMID and OSS on indicators such as the proportion of TB suspects tested for TB, proportion of TB patients who initiated and completed treatment, proportion of HIV positive mothers who were on ART and those that received ART medication at delivery as well as the proportion of HIV exposed babies who are given ART on delivery.

With regard to evaluating these effects in an integrated way, we use a mathematical HIV-TB model with age structure.

5.2 HIV-TB coinfection model

The non age structured HIV-TB model consists of 6 classes. There is a class of individuals susceptible (S) to HIV infection. A proportion, $(1-e)$ of these susceptible individuals (S) is fully susceptible to TB while the other proportion, e has latent TB.
Infection by HIV represented by λ_H occurs taking individuals to S_1, they get onto ART (at a rate $r_{_H}$) to move to S_2 and they fail ART at a rate $f_{_H}$.

Infection and reinfection by TB (λ_T) occurs for the individuals in the susceptible class sending them to the active TB class, I. Individuals with latent TB, a proportion e of the susceptible class also reactivate TB infection at a rate ν and move to I. Active TB people recover at a rate $r_{_T}$.
Individuals with active TB may also be infected with HIV to go to I_1, they get onto ART at a rate $r_{_H}$ and move to I_2.

Recruitment occurs by birth and is represented by terms, B and B_1. B is the recruitment for HIV negative people and B_1 accounts for HIV transmission at birth. HIV transmission through breast feeding is represented by $b_{_f}$.
The death rate of individuals is represented by μ with a subscript or without a subscript, the subscript stands for the class where the death is occurring.
FIG. 5.1 shows the model diagram and the model equations are given by (5.1a)–(5.1f).

$$\frac{dS}{dt} = B + r_{_T}I - b_f - (\lambda_{_H} + \lambda_{_T}e' + \nu e + \mu)S, \tag{5.1a}$$

$$\frac{dI}{dt} = (\lambda_{_T}e' + \nu e)S - (\lambda_{_H} + r_{_T} + \mu_{_I})I, \tag{5.1b}$$

$$\frac{dS_1}{dt} = B_1 + b_f + \lambda_{_H}S + f_{_H}S_2 + r_{_{T_1}}I_1 - (\lambda_{_T}e' + \nu_1 e + r_{_H} + \mu_{_{S_1}})S_1, \tag{5.1c}$$

$$\frac{dI_1}{dt} = \lambda_{_H}I + (\lambda_{_T}e' + \nu_1 e)S_1 + f_{_H}I_1 - (r_{_{T_1}} + r_{_{H_1}} + \mu_{_{I_1}})I_1, \tag{5.1d}$$

$$\frac{dS_2}{dt} = r_{_H}S_1 + r_{_{T_2}}I_2 - (f_{_H} + \lambda_{_T}e' + \nu_2 e + \mu_{_{S_2}})S_2, \tag{5.1e}$$

$$\frac{dI_2}{dt} = r_{_{H_1}}I_1 + (\lambda_{_T}e' + \nu_2 e)S_2 - (r_{_{T_2}} + f_{_H} + \mu_{_{I_2}})I_2, \tag{5.1f}$$

where:

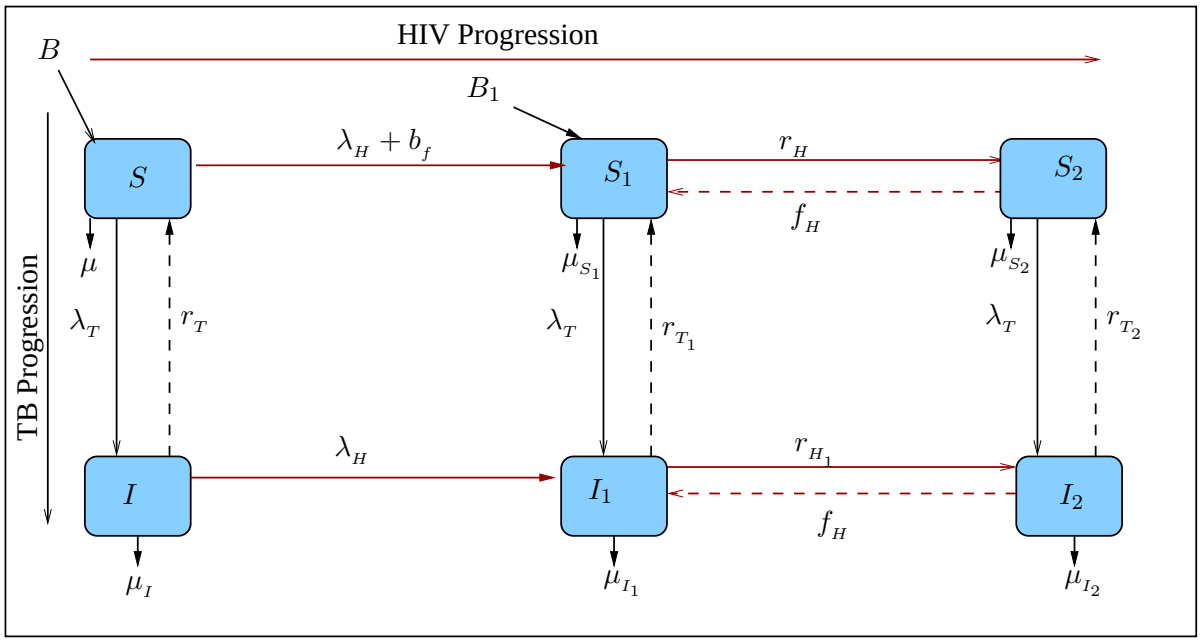


FIG. 5.1. HIV-TB model diagram

(i) $\lambda_H = \beta_H I_H/N$. β_H is the infection rate for HIV. $I_H = S_1 + I_1 + S_2 + I_2$ is the HIV infected human population and $N = S + I + S_1 + I_1 + S_2 + I_2$ is the total human population.

(ii) $\lambda_T = (\beta_T I + \beta_{TH}(I_1 + I_2))/N$. β_T is the rate at which individuals with active TB but no HIV pass on TB infection and β_{TH} is the rate at which coinfected HIV-TB individuals spread TB infection.

(iii) $e' = e_1(1 - e) + e_2 e$. e_1 and e_2 are the proportions of new infections and reinfections that progress to active TB.

It can be shown in a similar way as what was done with the malaria-pneumonia model in Chapter 4 that system (5.1a)–(5.1f) is biologically feasible in

$$\upsilon = \left\{(S, I, S_1, I_1, S_2, I_2) \in \Re_+^6 : S + I + S_1 + I_1 + S_2 + I_2 \leq \frac{B}{\mu}\right\}.$$

5.3 Mathematical analysis

This is carried out with the consideration that the parameters are constant.

5.3.1 Equilibrium points

These are time-independent states of a system. We determine them by setting the system of equations (5.1a)–(5.1f) to zero.

Disease Free Equilibrium (DFE^{HT})

This is the trivial equilibrium of the system where there is no infection in the population, that is $I = 0,\ S_1 = 0, I_1 = 0,\ S_2 = 0, I_2 = 0$ which exists if $B_1 = b_{_f} = e = 0$.
It is given as

$$\text{DFE}^{HT} = (B/\mu, 0, 0, 0, 0, 0).$$

The stability of the DFE^{HT} depends on the basic reproductive number, R_0^{HT}.

Basic reproduction number

It is computed following the same steps as discussed in Chapter 4. Let $\mathscr{F}$ be the vector formed by the rates of appearance of new infections and $\mathscr{V}$ be that formed by the rates of the transfers in and out of the compartments. The Jacobian matrices of $\mathscr{F}$ and $\mathscr{V}$ at DFE are given by:

$$\mathscr{F} = \begin{pmatrix} \lambda_{_T} e' S \\ B_1 + b_{_f} + \lambda_{_H} S \\ \lambda_{_H} I + \lambda_{_T} e' S_1 \\ 0 \\ \lambda_{_T} e' S_2 \end{pmatrix}, \quad \mathscr{V} = \begin{pmatrix} -\nu e S + (\lambda_{_H} + r_{_T} + \mu_{_I}) I \\ -f_{_H} S_2 - r_{_{T_1}} I_1 + (\lambda_{_T} e' + \nu_1 e + r_{_H} + \mu_{_{S_1}}) S_1 \\ -\nu_1 e S_1 - f_{_H} I_1 + (r_{_{T_1}} + r_{_{H_1}} + \mu_{_{I_1}}) I_1 \\ -r_{_H} S_1 - r_{_{T_2}} I_2 + (f_{_H} + \lambda_{_T} e' + \nu_2 e + \mu_{_{S_2}}) S_2 \\ -r_{_{H_1}} I_1 - \nu_2 e S_2 + (r_{_{T_2}} + f_{_H} + \mu_{_{I_2}}) I_2 \end{pmatrix}.$$

We find the derivatives of $\mathscr{F}$ and $\mathscr{V}$ at DFE: $e = 0$.

$$F = \begin{pmatrix} e_1\beta_{_T} & 0 & e_1\beta_{_{TH}} & 0 & e_1\beta_{_{TH}} \\ 0 & \beta_{_H} & \beta_{_H} & \beta_{_H} & \beta_{_H} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} r_{_T}+\mu_{_I} & 0 & 0 & 0 & 0 \\ 0 & r_{_H}+\mu_{_{S_1}} & -r_{_{T_1}} & -f_{_H} & 0 \\ 0 & 0 & -f_{_H}+r_{_{H_1}}+r_{_{T_1}}+\mu_{_{I_1}} & 0 & 0 \\ 0 & -r_{_H} & 0 & f_{_H}+\mu_{_{S_2}} & -r_{_{T_2}} \\ 0 & 0 & -r_{_{H_1}} & 0 & f_{_H}+r_{_{T_2}}+\mu_{_{I_2}} \end{pmatrix}.$$

R_0^{HT} is the spectral radius of FV^{-1}. Using mathematica, we obtain

$$R_0^{HT} = \max\{R_0^H, R_0^T\}$$

where:

$$\begin{aligned} R_0^H &= \frac{\beta_H(f_{_H}+r_{_H}+\mu_{_{S_2}})}{f_{_H}\mu_{_{S_1}}+(r_{_H}+\mu_{_{S_1}})\mu_{_{S_2}}}, \\ R_0^T &= \frac{e_1\beta_{_T}}{r_{_T}+\mu_{_I}}, \end{aligned}$$

are the reproduction numbers for HIV and TB respectively .

Local stability of the DFE

This is summarized in Theorem 5.3.1

Theorem 5.3.1 *If $B_1 = b_f = e = 0$, then the DFE^{HT} exists. Moreover if $R_0^{HT} < 1$, then DFE^{HT} is locally asymptotically stable.*

5.3.2 HIV sub model

The system of the HIV sub model is given by

$$\frac{dS}{dt} = B - b_f - (\lambda_{_H}+\mu)S, \tag{5.2a}$$

$$\frac{dS_1}{dt} = B_1 + b_f + \lambda_{_H}S + f_{_H}S_2 - (\mu_{_{S_1}}+r_{_H})S_1, \tag{5.2b}$$

$$\frac{dS_2}{dt} = r_{_H}S_1 - (f_{_H}+\mu_{S_2})S_2, \tag{5.2c}$$

Setting equations (5.2a)–(5.2c) to zero gives:

$$\begin{aligned} S^* &= \frac{B - b_f}{\mu + \lambda_H^*}, \\ S_1^* &= \frac{(\mu(b_f + B_1) + (B + B_1)\lambda_H^*)(f_H + \mu_{S_2})}{(\mu + \lambda_H^*)(f_H\mu_{S_1} + \mu_{S_2}(r_H + \mu_{S_1}))}, \\ S_2^* &= \frac{r_H(\mu(b_f + B_1) + (B + B_1)\lambda_H^*)}{(\mu + \lambda_H^*)(f_H\mu_{S_1} + \mu_{S_2}(r_H + \mu_{S_1}))}. \end{aligned}$$

Substituting, S^*, S_1^* and S_2^* into λ_H^* results into

$$C\lambda_H^{*2} + C_1\lambda_H^* + C_2 = 0, \tag{5.3}$$

where:

$$\begin{aligned} C &= (B + B_1)(f_H + r_H + \mu_{S_2}), \\ C_1 &= (f_H + r_H + \mu_{S_2})(\mu(b_f + B_1) - (B + B_1)) + (B - b_f)(\mu_{S_2}(r_H + \mu_{S_1}) + f_H\mu_{S_1}), \\ C_2 &= -\mu(b_f + B_1)\beta_H(f_H + r_H + \mu_{S_2}). \end{aligned}$$

From equation (5.3), it is clear that when $B_1 \neq 0$ and $b_f \neq 0$, then the system has one endemic equilibrium point (EEP^H) since C_2 is negative.

5.3.3 Stability of the EEP^H

For the local stability of the EEP^H, we use the centre manifold theorem from [32], stated in Theorem A.0.1.

We consider the case $R_0^H = 1$ and use $\beta_H = \beta_H^*$ as our bifurcation parameter. It is given as

$$\beta_H^* = \frac{f_H\mu_{S_1} + (r_H + \mu_{S_1})\mu_{S_2}}{f_H + r_H + \mu_{S_2}}.$$

The linearised system with $\beta_H = \beta_H^*$ has a zero eigenvalue which is simple and we can use the centre manifold theory to analyse the dynamics of the system near $\beta_H = \beta_H^*$.

Denote by $f = (f_1, f_2, f_3)^T$ the right hand side vector of (5.2a)–(5.2c). Following from Theorem A.0.1, we are required to compute values, a and b which we do by finding the

non-vanishing partial derivatives of f at DFE. All the necessary calculations are in appendix section A.3.

The values are given as:

$$\begin{aligned} a &= v_2 w_1 w_2 \frac{\beta_{_H}(B-\mu)}{B} + v_2 w_1 w_3 \frac{\beta_{_H}(B-\mu)}{B} + v_2 w_2 w_1 \frac{\beta_{_H}(B-\mu)}{B} - v_2 w_2^2 \frac{2\beta_{_H}\mu}{B} \\ &\quad - v_2 w_2 w_3 \frac{2\beta_{_H}\mu}{B} + v_2 w_3 w_1 \frac{\beta_{_H}(B-\mu)}{B} - v_2 w_3 w_2 \frac{2\beta_{_H}\mu}{B} - v_2 w_3^2 \frac{2\beta_{_H}\mu}{B}, \end{aligned}$$

w_1, w_2, w_3 and v_2 are defined in appendix section A.3.
Note that $B > \mu$, $v_2 > 0$, $w_1 < 0$, $w_2 > 0$, $w_3 > 0$. Therefore $a < 0$.

$$\begin{aligned} b &= v_2(w_2 + w_3), \\ &= \frac{f_{_H} + r_{_H} + \mu_{_{S_2}}}{f_{_H} + r_{_H} + \mu_{_{S_1}}} \left(\frac{f_{_H} + \mu_{_{S_2}}}{r_{_H}} + 1 \right). \end{aligned}$$

Clearly, $b > 0$.

From Theorem A.0.1, since $a < 0$ and $b > 0$, we have a positive endemic which is locally asymptotically stable. We also establish the following result.

Theorem 5.3.2 *If $R_0^H > 1$, an endemic equilibrium guaranteed by Theorem A.0.1 exists and is locally asymptotically stable.*

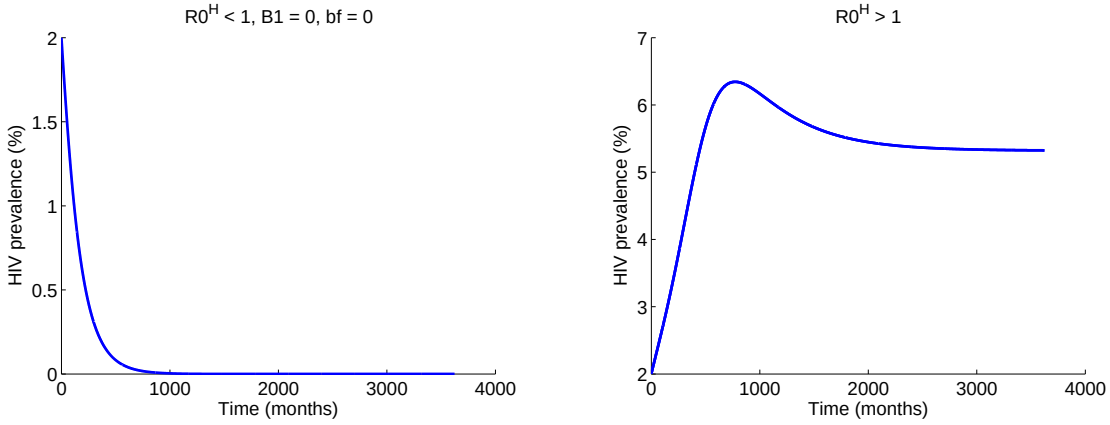
FIG. 5.2(a) and FIG. 5.2(b) show the numerical simulations for $R_0^H < 1$ and $R_0^H > 1$

5.3.4 TB sub model

The endemic equilibrium for the TB sub model is obtained as follows:

$$B + r_{_T} I - (\lambda_{_T} e' + \nu e + \mu) S = 0, \tag{5.4a}$$

$$(\lambda_{_T} e' + \nu e) S - (r_{_T} + \mu_{_I}) I = 0, \tag{5.4b}$$



(a) (b)

FIG. 5.2. Numerical simulations for R_0^H

where $\lambda_T = \beta_T I/N$, $e' = e_1(1-e) + e_2 e$. $N = S + I$ is the total population. The definitions of the parameters are in section 5.2.

Setting equations (5.4a)–(5.4b) and solving in terms of λ_T gives

$$\begin{aligned} S^* &= \frac{B(r_T + \mu_I)}{\mu r_T + (\mu + e\nu + e'\lambda_T^*)\mu_I}, \\ I^* &= \frac{B(e\nu + e'\lambda_T^*)}{\mu r_T + (\mu + e\nu + e'\lambda_T^*)\mu_I}, \end{aligned}$$

Substituting S^* and I^* into λ_T yields equation 5.5.

$$\lambda_T^{*2} + \frac{(e\nu + r_T + \mu_I - \beta_T e')}{e'}\lambda_T^* - \frac{\beta_T e\nu}{e'} = 0, \tag{5.5}$$

We then consider two cases

Case 1: $e = 0$

When $e = 0$, equation 5.5 becomes

$$\lambda_T^*(\lambda_T^* + \frac{r_T + \mu_I}{e'}(1 - R_0^{TB})) = 0,$$

which gives $\lambda_T^* = 0$, the DFE equilibrium and $\lambda_T^* = \frac{r_T+\mu_I}{e'}(R_0^{TB} - 1)$ which only exists iff $R_0^{TB} > 1$.

This implies that if there are no individuals with latent TB, then the endemic equilibrium exists only if the reproductive number is greater than 1.

Case 2: $e \neq 0$

When $e \neq 0$, we have equation 5.5

$$\lambda_T^{*2} + \frac{(e\nu + r_T + \mu_I - \beta_T e')}{e'}\lambda_T^* - \frac{\beta_T e\nu}{e'} = 0,$$

which has one positive endemic equilibrium.

Local stability of EEP^T

To establish the local stability of the endemic equilibrium, we make use of the centre manifold theorem stated in Theorem A.0.1.

We denote the right hand side of system (5.4a)–(5.4b) by $f = (f_1, f_2)^T$. We consider the case when $R_0^{TB} = 1$ and take $\beta_T = \beta_T^*$ as our bifurcation parameter. It is given as

$$\beta_T^* = \frac{r_T + \mu_I}{e_1}.$$

The linearised system with $\beta_T = \beta_T^*$ has a zero eigenvalue which is simple.
We can use the centre manifold theory to analyse the dynamics of the modified system near $\beta_T = \beta_T^*$ and in particular we can determine the local stability of the endemic equilibrium of system (5.4a)–(5.4b).

We then compute a and b by finding the non-zero partial derivatives of f at DFE. All the calculations are in appendix section A.4. Thus

$$a = e_1\beta_T\mu_T\left(\frac{1}{\mu} - \frac{1}{B}\right) + \frac{2e_1\beta_T\mu}{B}.$$

Since $B > \mu$, then $a > 0$.

$$b = \frac{e_1\mu}{B}.$$

We have $b > 0$.

From Theorem A.0.1, we have a subcritical (backward) bifurcation at $R_0^{TB} = 1$ and we establish the following result.

Theorem 5.3.3 *An endemic equilibrium guaranteed by Theorem A.0.1 exists and is locally asymptotically stable when $R_0^{TB} < 1$ but close to 1.*

This result raises an important point, that for effective eradication of TB, it is not only sufficient that R_0^{TB} to be less than one but that it must be smaller than a certain critical value less than one.

FIG. 5.3(a), FIG. 5.3(b) and FIG. 5.3(c) show the numerical simulations for $R_0^T < 1$ and $R_0^T > 1$ with $e = 0$ and $e \neq 0$.

The implications of the mathematical analysis carried out for the non-age structured HIV-TB model with constant parameters on the model with time dependent parameters are discussed in section 4.4.

5.4 HIV-TB model with age structure

The model of HIV-TB with age structure is an extension of the one in section 5.2. It is divided into three age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$. Individuals age from $[0, 5)$ to $[5, 14)$ at a rate η_1, from $[5, 14)$ to $[14, 50)$ at a rate η_2 and out of $[14, 50)$ at a rate η_3. The parameters in this model are defined similarly as the ones in the model without age structure except that they now have subscript $j = c,\ b,\ a$ representing $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively.

Important to note is that:

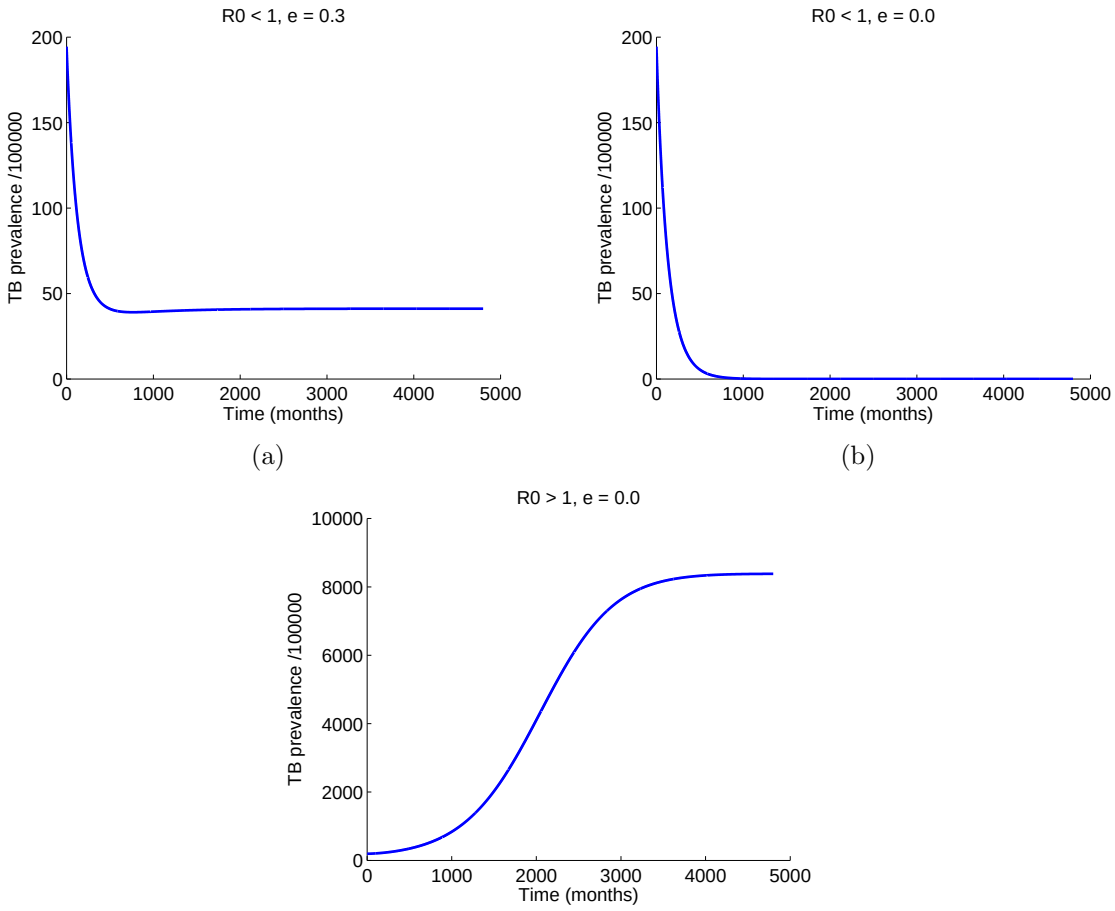


FIG. 5.3. Numerical simulations for R_0^T

(i) We have two kinds of transmission of HIV, mother to child transmission both at birth (B_1) or through breastfeeding, $b_f(t)$ and HIV transmission (λ_H) between individuals in the $[14, 50)$ age group.

(ii) There is no HIV transmission in the $[5, 14)$ age group but we have some HIV infected individuals from the $[0, 5)$ who age into the $[5, 14)$ age group.

(iii) We also assume that HIV negative babies born to HIV positive mothers only get infected through breastfeeding and none of these babies develops active TB before infection with HIV.

Considering model diagram FIG. 5.1, the model diagram for the $[0, 5)$ age group does not have the HIV transmission term λ_H and there is no movement from I_c to I_{1_c}. The rest of

the in and out flows stay the same.
Model diagram for $[5, 14)$ has no birth terms and no HIV transmission terms but the other flows in and out are the same.
The diagram for $[14, 50)$ has no birth terms, no HIV transmission through breastfeeding but HIV transmission given by $\lambda_{_H}$ and the rest of the flows in and out are the same.
The model equations are given by set of equations (5.6a)–(5.6f) for the $[0, 5)$ age group, (5.7a)–(5.7f) for the $[5, 14)$ and (5.8a)–(5.8f) for the $[14, 50)$ age group.

$$\frac{dS_{_c}}{dt} = B + r_{_T} I - b_f(t) - (\lambda_{_{T_c}} e'_c + \nu e_c + \mu_{_c} + \eta_1) S_{_c}, \tag{5.6a}$$
$$\frac{dI_{_c}}{dt} = (\lambda_{_{T_c}} e'_c + \nu e_c) S_{_c} - (r_{_T} + \mu_{_{I_c}} + \eta_1) I_{_c}, \tag{5.6b}$$
$$\frac{dS_{1_c}}{dt} = B_1 + b_f + f_{_H} S_{2_c} + r_{_{T_1}} I_{1_c} - (\lambda_{_{T_c}} e'_c + \nu_1 e_c + r_{_H} + \mu_{_{S_{1_c}}} + \eta_1) S_{1_c}, \tag{5.6c}$$
$$\frac{dI_{1_c}}{dt} = (\lambda_{_{T_c}} e'_c + \nu_1 e_c) S_{1_c} + f_{_H} I_{1_c} - (r_{_{T_1}} + r_{_H} + \mu_{_{I_{1_c}}} + \eta_1) I_{1_c}, \tag{5.6d}$$
$$\frac{dS_{2_c}}{dt} = r_{_H} S_{1_c} + r_{_{T_2}} I_{2_c} - (f_{_H} + \lambda_{_{T_c}} e'_c + \nu_2 e_c + \mu_{_{S_{2_c}}} + \eta_1) S_{2_c}, \tag{5.6e}$$
$$\frac{dI_{2_c}}{dt} = r_{_{H_1}} I_{1_c} + (\lambda_{_{T_c}} e'_c + \nu_2 e_c) S_{2_c} - (r_{_{T_2}} + f_{_H} + \mu_{_{I_{2_c}}} + \eta_1) I_2, \tag{5.6f}$$

$$\frac{dS_{_b}}{dt} = \eta_1 S_{_c} + r_{_T} I_{_b} - (\lambda_{_{T_b}} e'_b + \nu e_b + \mu_{_b} + \eta_2) S_{_b}, \tag{5.7a}$$
$$\frac{dI_{_b}}{dt} = \eta_1 I_{_c} + (\lambda_{_{T_b}} e'_b + \nu e_b) S - (r_{_T} + \mu_{_{I_b}} + \eta_2) I_{_b}, \tag{5.7b}$$
$$\frac{dS_{1_b}}{dt} = \eta_1 S_{1_c} + f_{_H} S_{2_b} + r_{_{T_1}} I_1 - (\lambda_{_{T_b}} e'_b + \nu_1 e_b + r_{_H} + \mu_{_{S_{1_b}}} + \eta_2) S_{1_b}, \tag{5.7c}$$
$$\frac{dI_{1_b}}{dt} = \eta_1 I_{1_c} + (\lambda_{_{T_b}} e'_b + \nu_1 e_b) S_{1_b} + f_{_H} I_{2_b} - (r_{_{T_1}} + r_{_H} + \mu_{_{I_{1_b}}} + \eta_2) I_{1_b}, \tag{5.7d}$$
$$\frac{dS_{2_b}}{dt} = \eta_1 S_{2_c} + r_{_H} S_{1_b} + r_{_{T_2}} I_{2_b} - (f_{_H} + \lambda_{_{T_b}} e'_b + \nu_2 e_b + \mu_{_{S_{2_b}}}) S_{2_b}, \tag{5.7e}$$
$$\frac{dI_{2_b}}{dt} = \eta_1 I_{2_c} + r_{_{H_1}} I_{1_b} + (\lambda_{_{T_b}} e'_b + \nu_2 e_b) S_{2_b} - (r_{_{T_2}} + f_{_H} + \mu_{_{I_{2_b}}} + \eta_2) I_{2_b}, \tag{5.7f}$$

$$\frac{dS_a}{dt} = \eta_2 S_b + r_T I_a - (\lambda_H + \lambda_{T_a} e'_a + \nu e_a + \mu_a + \eta_3) S_a, \tag{5.8a}$$

$$\frac{dI_a}{dt} = \eta_2 I_b + (\lambda_{T_a} e'_a + \nu e_a) S_a - (\lambda_H + r_T + \mu_{I_a} + \eta_3) I_a, \tag{5.8b}$$

$$\frac{dS_{1_a}}{dt} = \eta_2 S_{1_b} + \lambda_H S_a + f_H S_{2_a} + r_{T_1} I_{1_a} - (\lambda_{T_a} e'_a + \nu_1 e_a + r_H + \mu_{S_{1_a}}) S_{1_a} - \eta_3 S_{1_a}, \tag{5.8c}$$

$$\frac{dI_{1_a}}{dt} = \eta_2 I_{1_b} + \lambda_H I_a + (\lambda_{T_a} e'_a + \nu_1 e_a) S_{1_a} + f_H I_{2_a} - (r_{T_1} + r_H + \mu_{I_{1_a}}) I_{1_a} - \eta_3 I_{1_a}, \tag{5.8d}$$

$$\frac{dS_{2_a}}{dt} = \eta_2 S_{2_b} + r_H S_{1_a} + r_{T_2} I_{2_a} - (f_H + \lambda_{T_a} e'_a + \nu_2 e_a + \mu_{S_{2_a}} + \eta_3) S_{2_a}, \tag{5.8e}$$

$$\frac{dI_{2_a}}{dt} = \eta_2 I_{2_b} + r_{H_1} I_{1_a} + (\lambda_{T_a} e'_a + \nu_2 e_a) S_{2_a} - (r_{T_2} + f_H + \mu_{I_{2_a}} + \eta_3) I_{2_a}, \tag{5.8f}$$

where:

(i) $\lambda_H = \beta_H I_H / N$. β_H is the infection rate for HIV. I_H is the HIV infected human population and N is the total human population.

(ii) $\lambda_{T_c} = (\beta_{T_c} I_T + \beta_{TH_c} I_{TH})/N$. β_{T_c} is the rate at which HIV negative active TB individuals pass on infection to individuals in the $[0, 5)$ age group. β_{TH_c} is the rate at which HIV-TB coinfected individuals pass on infection to individuals in the $[0, 5)$ age group. Similar definitions hold for the $[5, 14)$ and $[14, 50)$ age groups with the infection term being represented by subscripts b and a respectively.

(iii) $e'_c = e_{1c}(1 - e_c) + e_{2c} e_c$. e_{1c} and e_{2c} are the proportions of new infections and reinfections that progress to active TB in the $[0, 5)$ age group. Similar definitions hold for the $[5, 14)$ and $[14, 50)$ age groups with the proportions of new infections and reinfections being represented by subscripts b and a accordingly.

5.5 Formulations, parameter values from literature

In this section, we discuss various parameters for HIV, TB and HIV-TB coinfection and give values obtained from literature.

5.5.1 HIV parameters

HIV positive births, B_1

Suppose that ρ_1, ρ_2, ρ_3 and ρ_4 are the crude per capita birth rates for HIV negative individuals, HIV positive individuals unaware of their status, HIV positive individuals aware of their status but are not on ART or not on PMTCT and those on ART or PMTCT respectively (Please note that the effect of ART and PMTCT is not differentiated).
The birth rates of these groups are different. Fertility is reduced in HIV positive individuals [66, 207] and being on ART increases the chances of wanting a child though it is still not equal to those individuals who are HIV negative [35, 114]. Using $\rho_2 = 0.8\rho_1$ [66] and $\rho_4 = 1.877\rho_3$ [114] and taking ρ as the total crude birth rate of the whole population, we calculate ρ_1 and ρ_3. Thus we have $\rho_1 = \frac{\rho}{(1-p_{_H})+(0.8*p_{_H})}$ and $\rho_3 = \frac{\rho_2}{(1+0.877k\gamma_1)}$, where $p_{_H}$ is the proportion of individuals with HIV, k is the proportion of HIV positive individuals on ART/PMTCT and γ_1 is the proportion of individuals tested.

Among the population giving birth, a constant proportion, γ_1 is tested. Of those found HIV positive, a proportion, k receive ART. The risk of transmission for HIV positive individuals not on ART/PMTCT is (ϕ_1) and for those on ART/PMTCT, it is (ϕ_2).
Thus we have:

- The number of births per unit time from HIV negative people is given as

$$\rho_1 N_{_{H-}}.$$

  where $N_{_{H-}}$ is the HIV negative population.

- The number of births per unit time from HIV positive people unaware of their status is given by:

$$(1-\gamma_1)\rho_2 N_{_{H+}}.$$

  where $N_{_{H+}}$ is the HIV positive population

- Births for HIV positive people tested not on ART/PMTCT are:

$$(1-k)\gamma_1\rho_3 N_{_{H+}}.$$

- Then, births for HIV positive people tested and on ART/PMTCT are given by:

$$k\gamma_1\rho_4 N_{H+}.$$

Using the risks of transmission, we have the number of HIV positive babies at birth being,

$$B_1 = (\phi_1(1-\gamma_1)\rho_2 + (\phi_1(1-k)\rho_3 + \phi_2 k\rho_4)\gamma_1)N_{H+}$$

and the number of HIV negative babies from HIV positive mothers is

$$B_2 = ((1-\phi_1)(1-\gamma_1)\rho_2 + ((1-\phi_1)(1-k)\rho_3 + (1-\phi_2)k\rho_4)\gamma_1)N_{H+}.$$

Accounting for the number of HIV negative babies, we obtain

$$B = \rho_1 N_{H-} + B_2.$$

The risk of transmission of HIV at birth for mothers not on ART varies from 15% to 50% [49, 183, 185, 197] and the for mothers on ART, this risk is reduced by 30% to 75% [41, 183, 185, 197] giving a risk of transmission between 4% and 35%.
In the model we consider the risk of transmission of HIV at birth for mothers not on ART/PMTCT to be 30% for those on ART/PMTCT to be 5%. These parameter values and their references are summarized in TABLE. 5.1.

HIV transmission through breastfeeding

At each point in time, the number of HIV negative children born to HIV positive mothers increases by $B_2 = ((1-\phi_1)(1-\gamma_1)\rho_2 + ((1-\phi_1)(1-k)\rho_3 + (1-\phi_2)k\rho_4)\gamma_1)N_{H+}$. Of these, a proportion, p_{bf} is breastfed which increases their risk of acquiring HIV. Moreover, the risk of MTCT through breastfeeding differs when there is no ART/PMTCT, φ_1, to when there is ART/PMTCT, φ_2. Hence, we consider that a proportion, p_A of these children receive ART/PMTCT and the other proportion does not.

The number of children who would get infected with HIV through breastfeeding at a point in time is given as CN_{H+} where $C = (\varphi_1(1-p_A) + \varphi_2 p_A)B_2 p_{bf}$.

We used breastfeeding data of Uganda from Spectrum which gives the proportion of children breastfeeding from birth up to three years and we considered this to be the probability

of still being breastfed. FIG. 5.4 shows this data fitted to a Weibull function $\psi(t) = e^{-\lambda t^{\delta}}$, where t is the age of the baby with $\lambda = 0.06$ as the shape parameter and $\delta = 4.18$, the scale parameter. These parameter values and their references have been summarized in TABLE. 5.1.

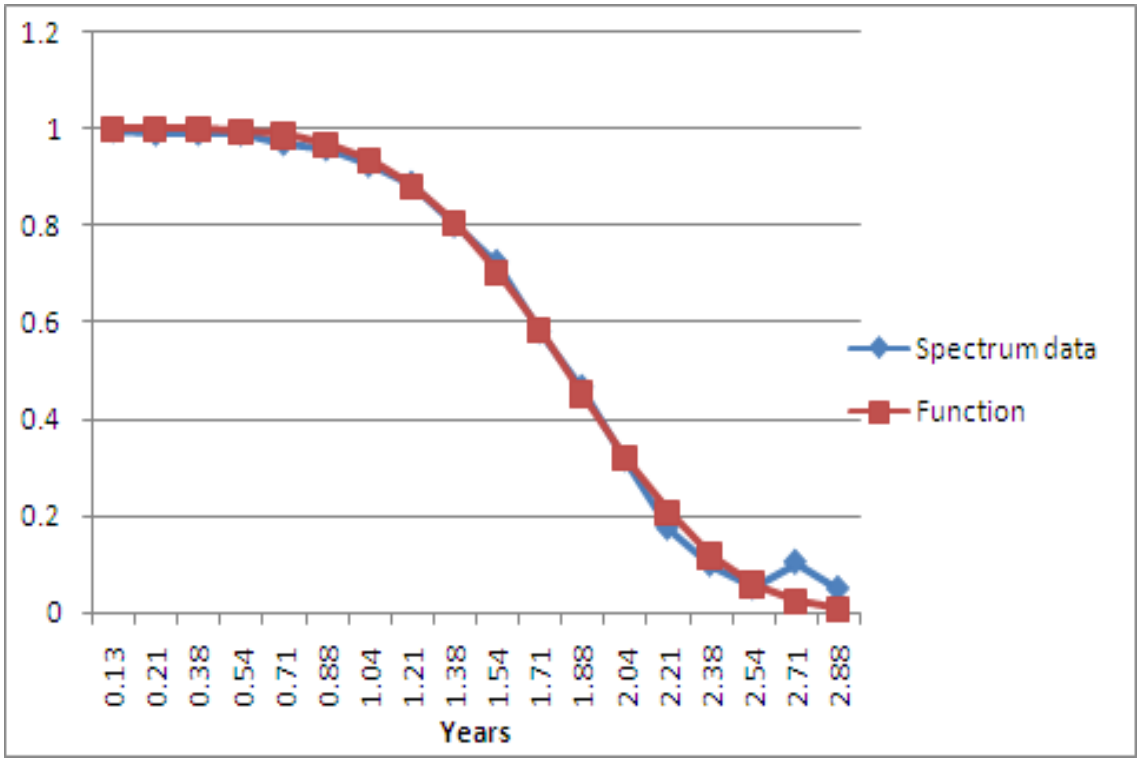


FIG. 5.4. Probability of still being breastfed

Given that the death rate μ_c of children is constant, the probability of surviving until age t is given by $e^{-\mu_c t}$.

Putting all this into consideration, we have the number of children born to HIV positive mothers who are breastfeeding children at time, t as:

$$\int_{-\infty}^{t} \psi(t-s) e^{-\mu_c (t-s)} C N_{H+}(s)\, \mathrm{d}s.$$

The expression above involves an infinite delay, and knowing that the probability of being breastfed is small for ages higher than 3 years, we approximate the infinite delay integral as

$$\int_{t-\tau}^{t} \psi(t-s) e^{-\mu_c (t-s)} C N_{H+}(s)\, \mathrm{d}s.$$

with τ large enough.
We define $G(t,s) = \psi(t-s)e^{-\mu_c(t-s)}CN_{H+}(s)$. This equation implies that the model is an integro-differential equation with delay.

When $t < \tau$, the above expression involves the history of the N_{H+}. Thus, we split the integral as follows:

$$\int_{t-\tau}^{t} G(t,s)\,\mathrm{d}s \;=\; \int_{t-\tau}^{0} G(t,s)\,\mathrm{d}s + \int_{0}^{t} G(t,s)\,\mathrm{d}s$$

For our particular case, we assume that $N_{H+}(s) = N_{H+}(0)$ for $-\tau \leq s \leq 0$ where $N_{H+}(0)$ is the initial value of $N_{H+}(s)$.
Thus the number of children born to HIV positive mothers who are still being breastfed at time t is given by

$$\int_{t-\tau}^{t} G(t,s)\,\mathrm{d}s \;=\; \bar{N}_{H+}\bar{G}(t,s) + \int_{0}^{t} G(t,s)\,\mathrm{d}s.$$

where $\bar{G}(t,s) = \int_{t-\tau}^{0} C\psi(t-s)e^{-\mu_c(t-s)}ds$ and $\bar{N}_{H+} = N_{H+}(0)$.

Cotrimoxazole prophylaxis (CTX) uptake

CTX is given to HIV positive individuals and it reduces their mortality and morbidity rates [193]. It is modelled implicitly by reducing, in individuals on CTX, the mortality rate (μ_{S_1}) and the proportion of HIV positive individuals who progress to active TB.
It is important to note that these individuals are aware of their HIV status. We define γ as the proportion that are tested and p_s is the proportion of HIV positive individuals on CTX.
Considering S_1, the number of HIV positive individuals on CTX is given as $\gamma p_s S_1$ and that not on CTX is given as $(1-\gamma p_s)S_1$.

TABLE. 5.1. Parameters of MTCT and births

Parameter	Description	Value	Reference
ρ	Crude birth rate	0.0423	Chosen [85, 148, 149]
ϕ_1	Risk of mother-to-child transmission (MTCT) at birth - no ART	30% (14% – 42%)	[49, 137, 183, 197]
ϕ_2	Risk of MTCT at birth - with ART	5% (4.5% – 15%)	[137, 197]
φ_1	Risk of MTCT through breastfeeding - no ART	15% (5% – 20%)	[43, 142, 197]
φ_2	Risk of MTCT through breastfeeding - with ART	5% (2.5% – 10%)	[73, 188]
$\psi(\alpha, \lambda)$	λ = 0.06-shape parameter and δ = 4.18-scale parameter. Function gives the probability that a child is being breastfed	$\psi(4.18, 0.06)$	Spectrum data [87]
$p_{_{bf}}$	proportion of children from HIV positive mothers who breastfeed	0.91	[137]

ART enrollment and failure rates

The ART enrollment rate, $r_{_H}$ can be obtained by using the fraction of HIV positive individuals that go onto ART:

$$A_{_f} = \frac{r_{_H}\gamma S_1}{r_{_H}\gamma S_1 + (\mu_{_{S_{1_0}}}(1-\gamma p_{_s}) + \mu_{_{S_{1_1}}}\gamma p_{_s})S_1}.$$

where 0 and 1 subscripts for $\mu_{_{S_1}}$ represent not on and on cotrimoxazole respectively. Thus,

$$r_{_H} = \frac{A_{_f}(\mu_{_{S_{1_0}}}(1-\gamma p_{_s}) + \mu_{_{S_{1_1}}}\gamma p_{_s})}{\gamma(1-A_{_f})}.$$

This expression corresponds to that in [11, 23].

By end of 2009, the percentage of individuals, both adults and children in need of ART was 54% as per national guidelines of a cut off of CD4-T cell count less than 250 cells

per microlitre and the proportion of these receiving ART was 53.5% [40, 199]. Using both these values gives 0.29 as the proportion of all HIV positive individuals on ART.

For our study population, the proportion of eligible HIV positive individuals receiving ART is lower than the national average. Considering information in TABLE 3.6, the average proportion of adults initiating ART treatment is calculated as 0.27 (using the proportion enrolled into HIV care, the proportion that receives ART and the respective proportions for pregnant women and HIV-TB coinfected individuals in the HIV population). Thus considering all HIV positive individuals in our study population and using the proportion in need of ART as 0.54 [40], we calculate the proportion of HIV positive adults on ART as 0.15.
In [40], of the patients on ART, 8.5% were children (< 15 years) and the other percentage, 91.5% were adults (> 15 years). This means that in our study population only about 1.3% of HIV positive children are on ART.

We thus choose the fraction of HIV positive adults starting ART so as to end up with the proportion of HIV positive adults on ART as being 0.15. For the $[0, 5)$ and $[5, 14)$, the fractions we choose are such that we end up with the proportion of HIV positive children on ART as being about 1.3% in either age group. We chose different fractions for HIV positive individuals without TB and for HIV-TB coinfected individuals for the three age groups, $[0, 5)$, $[5, 14)$ and $[14, 50)$. For HIV positive individuals without TB, the fractions are: $4/10000$ for the $[0, 5)$, $9/100000$ for the $[5, 14)$ and $245/10000$ for the $[14, 50)$ age group.
For HIV-TB coinfected individuals, these fractions are: $4/100$ for the $[0, 5)$, $9/1000$ for the $[5, 14)$ and $25/100$ for the $[14, 50)$ age group.

Some individuals on ART will fail ART due to some side effects. Failure of ART can occur when immunological or virological failure occurs. Immunological outcomes consist of CD4 cell count measurements while virological outcomes are obtained by measuring the viral load. Immunological failure is what is commonly and currently considered when investigating ART failure though it is also important to consider virological failure. In [89, 159, 162], the rates of virological failure ranged from 0.05 to 0.09 per year. The rates of immunological failure ranged from 0.0034 to 0.08 per year [159, 162]. In [11], the rate of ART failure (rate at which individuals drop out of ART programme) was taken to be

0.015. For our model, we use 0.03 per year.

HIV infection and death rates

The HIV infection rate, β_H, is obtained by calibrating the incidence, $\beta_H I_H/N$ to that from Spectrum [87]. We input the incidence from Spectrum reduced by a factor to result into an HIV prevalence of 5.4% that is observed in the population under study.

Death rates due to HIV infected individuals not on ART were calculated in a similar way as the natural death rates in Chapter 3 using population numbers from Spectrum (DemProj and AIM) [87] with default Uganda country data.
As a comparison, in [88], the mortality rate for HIV positive adults was given as 0.049 which is not different from the one calculated from Spectum, of 0.047 for the $[14, 50)$ age group. The death rates for HIV infected individuals not on ART are summarized in TABLE. 5.2.

Mortality rates for HIV positive individuals on ART and on CTX are obtained from a number of studies. The death rate of individuals on ART differs depending on how long the individual has been on ART and what CD4 cell count they had when initiating ART. In [126], the death rate of individuals initiating ART ranged from 0.0538 in those with a CD4 cell count of less than 50 to 0.0157 for those with at least 300 CD4 cell count.
In [125], the mortality rate of HIV positive adults on ART was given as 0.0318. For our model, we are interested in the average death rate of HIV positive individuals on ART and thus we use the one in [125] for the $[14, 50)$ age group. For the age groups $[5, 14)$ and $[0, 5)$, we use the death rates given in [12] and these are: 0.0365 for adolescents and 0.0228 for children.
The total death rates are a summation of these HIV specific death rates with the natural death rates (in TABLE. 4.4) and they are reported in TABLE 5.2.
For HIV positive individuals on CTX, there is 30% to 50% reduction in the death rate [79, 121, 157].

In addition, ART and CTX not only reduce the mortality rates of HIV positive individuals, but also reduce their morbidity. ART is known to reduce the morbidity of HIV positive individuals eligible for ART by 53% and CTX reduces their morbidity by 35% [123].

5.5.2 TB parameters for HIV negative people

Infection and reinfection

It is estimated that an active TB person infects about 10 to 14 people per year [10]. Given that we have age groups, there is limited literature on the infection rates for individuals in different age groups.
For our model, we chose the infection rate for the $[0, 5)$ age group as 0.25 per year, 0.05 per year for the $[5, 14)$ age group, and for $[14, 50)$, we used 7.0 per year. These were chosen in accordance to maintaining a reasonable TB prevalence of 280 per 100000 for adults and 12 per 100000 for the $[0, 5)$ and $[5, 14)$.
The reinfection rates are the same as the infection rates except that progression to disease is reduced by 33% if it is a reinfection. In [10], a 30% reduction was considered with reinfection.

Progression to disease and reactivation

The rate of progression of disease is a decreasing function of time since infection. In [192], the cumulative risk of progression to disease after 5 years of infection was estimated to be 14%, and 4% for individuals of ages $[0, 10]$, and 9% for individuals aged 15.
Individuals in the age group $[5, 14)$ have a lower risk of progressing to disease and they are sometimes called the 'golden age group' [109, 211].
We do not include time since infection in our model, but we consider that a constant proportion of individuals, e_1 develop active TB after infection and a proportion, e_2 develop disease after reinfection. We have different values of these proportions for the different age groups and they are differentiated by subscripts, c, b and a which represent the age groups $[0, 5)$, $[5, 14$ and $[14, 50)$. The values of the proportions are stated in TABLE 5.2.

The rate of reactivation ranges from 0.0001 to 0.00074 [10, 30, 192] in individuals who are HIV negative. The values of rates of reactivation for the different age groups are given in TABLE. 5.2.

Treatment and recovery

Individuals with active TB may recover naturally at a rate 0.2 per year [10] and when they receive treatment and complete it successfully, they recover at a rate ranging from 12/6 to 12/8 per year depending on the duration of treatment [52, 134]. However, there are other conditions that determine the recovery such as the patient reporting to the clinic, getting a TB diagnosis, receiving medication and completing the medication. The recovery rate for TB is fully defined in subsection 3.2.3.

Death rate

The death rate of TB for the Ugandan population was 29/100000 population per year in 2009 [200, 212]. Taking into consideration that the prevalence of TB in Uganda in 2009 was given as 277/100000 population [200]. We calculate the death rate of TB individuals as 29/277 which is 0.105 per TB case per year. [10] also gives some values for the death rate of TB cases.

5.5.3 Parameters of HIV-TB coinfection

The parameters for HIV-TB coinfection are influenced mainly by HIV.

Infection and reinfection

HIV positive people are more susceptible to TB infection and reinfection [190]. Moreover, most HIV infected patients have fewer bacilli in their sputum and have more extrapulmonary tuberculosis than HIV-negative patients [10, 33, 38, 48]. For this reason, HIV infected patients are less infectious than HIV-negative patients with active tuberculosis. We take that the rate at which HIV-TB coinfected individuals infect others is reduced by 33% as in [10].

Progression to disease and reactivation

As compared to HIV negative individuals, HIV positive ones have a higher risk of progression to active TB [33, 211].
While the risk of progression of HIV negative individuals infected with TB is 10% for their lifetime, that of individuals coinfected with both HIV and TB is 10% per year [33]. About 70% of all HIV-infected individuals develop active TB [33, 191].

The reactivation rate of individuals with HIV-TB coinfection ranges from 40 to 500 times that of individuals infected with TB only [95, 198]. For our model, we take the reactivation rate of HIV-TB coinfected individuals to be 80 times more than that of individuals infected with TB but without HIV infection. We also consider that the reactivation rate for individuals who are on ART reduces by 5 times that of HIV-TB coinfected individuals not on ART.

Death rate

It has been noted that individuals with coinfection of TB and HIV have a death rate that is 6 times higher than that of individuals with HIV only [10] and this is what we use for our model simulations.

5.6 Model simulations

We run the model with baseline values before we incorporate in the effect of the interventions. All the numerical simulations are generated using the HIV-TB model with age structure (refer to section 5.4).

Uganda HIV prevalence was about 6.4% in 2006 in adults and 0.7% in children less than 15 years of age [39]. The sites that IDCAP considered have a lower HIV prevalence because most of them are in rural areas. We calculated the HIV prevalence in adults as being 5.4% using prevalence data from Uganda's sentinel sites in [40].
We inputed HIV incidence from Spectrum [87] with default Uganda data and reduced it by a factor (we multiplied it by 0.85) until it gave a prevalence of 5.4% (refer to subsection

TABLE. 5.2. Parameters for HIV, TB, HIV-TB

Parameter	Description	Value	Reference
$\mu_{S_{1_c}}$, $\mu_{S_{1_b}}$, $\mu_{S_{1_a}}$	HIV death rates for individuals who are not on ART for corresponding age groups.	0.166, 0.064,0.065	Spectrum [87], [88]
$\mu_{S_{2_c}}$, $\mu_{S_{2_b}}$, $\mu_{S_{2_a}}$	HIV death rates for individuals who are on ART for corresponding age groups.	0.0488, 0.0405, 0.048	[12, 125, 126, 129]
e_c, e_b, e_a	Proportion with latent TB	0.05, 0.2, 0.52	Chosen to end up with overall proportion with latent TB as being 33%
e_{1c}, e_{1b}, e_{1a}	Proportion of new infections that develop active TB	0.1, 0.025, 0.05	[10, 192]
ν, ν_1, ν_2	Reactivation rates for TB positive-HIV negative, HIV-TB coinfected not on ART and HIV-TB coinfected on ART	0.0003, 0.0228, 0.0114	[10, 30, 33, 198]
μ_{I_c}, μ_{I_b}, μ_{I_a}	Death rates due to TB	0.105	Calculated [10]

5.5.1 under HIV infection and death rates).

We use 52% as the proportion of HIV in TB cases. In [203], it was given as 54% and it takes values of 50% or more in other studies [10].

The TB prevalence in adults was 0.3% in 2005 and fell to 0.2% in 2009 [200]. We use a TB prevalence of 280/100000 for adults at baseline.
For age groups $[0, 5)$ and $[5, 14)$, we take note of [6], where it is stated that about 5% to 6% of annual TB cases are among children less than 15 years of age with 60% of these being in children under 5 years of age. With this insight, we use a TB prevalence of 12/100000

for the two age groups, $[0, 5)$ and $[5, 14)$.

For the initial conditions, we use the following numbers.

$$S_{_c}(0) = 6968,\ S_{1_c}(0) = 47,\ S_{2_c}(0) = 1,\ I_{_c}(0) = 1,\ I_{1_c} = 0.15,\ I_{2_c} = 0.001$$

$$S_{_b}(0) = 9881,\ S_{1_b}(0) = 51,\ S_{2_b}(0) = 1,\ I_{_b}(0) = 1,\ \ I_{1_b} = 0.3,\ I_{2_b} = 0.002$$

$$S_{_a}(0) = 17987,\ S_{1_a}(0) = 856,\ S_{2_a}(0) = 154,\ I_{_a}(0) = 25,\ \ I_{1_a} = 24,\ I_{2_a} = 4.0$$

These values correspond to the steady states of the model without interventions. The I_{1_c}, I_{2_c}, I_{1_b} and I_{2_b} are set as such so that the proportion of HIV in TB cases does not appear as being zero initially.

For the model simulations, we use parameters in TABLE.5.1, TABLE. 5.2, TABLE. 3.5 and TABLE. 3.6.
The graphs for model simulations at baseline are in FIG. 5.5(a), FIG. 5.5(b), FIG. 5.5(c), FIG. 5.5(d), FIG. 5.6(a) and FIG. 5.6(b).

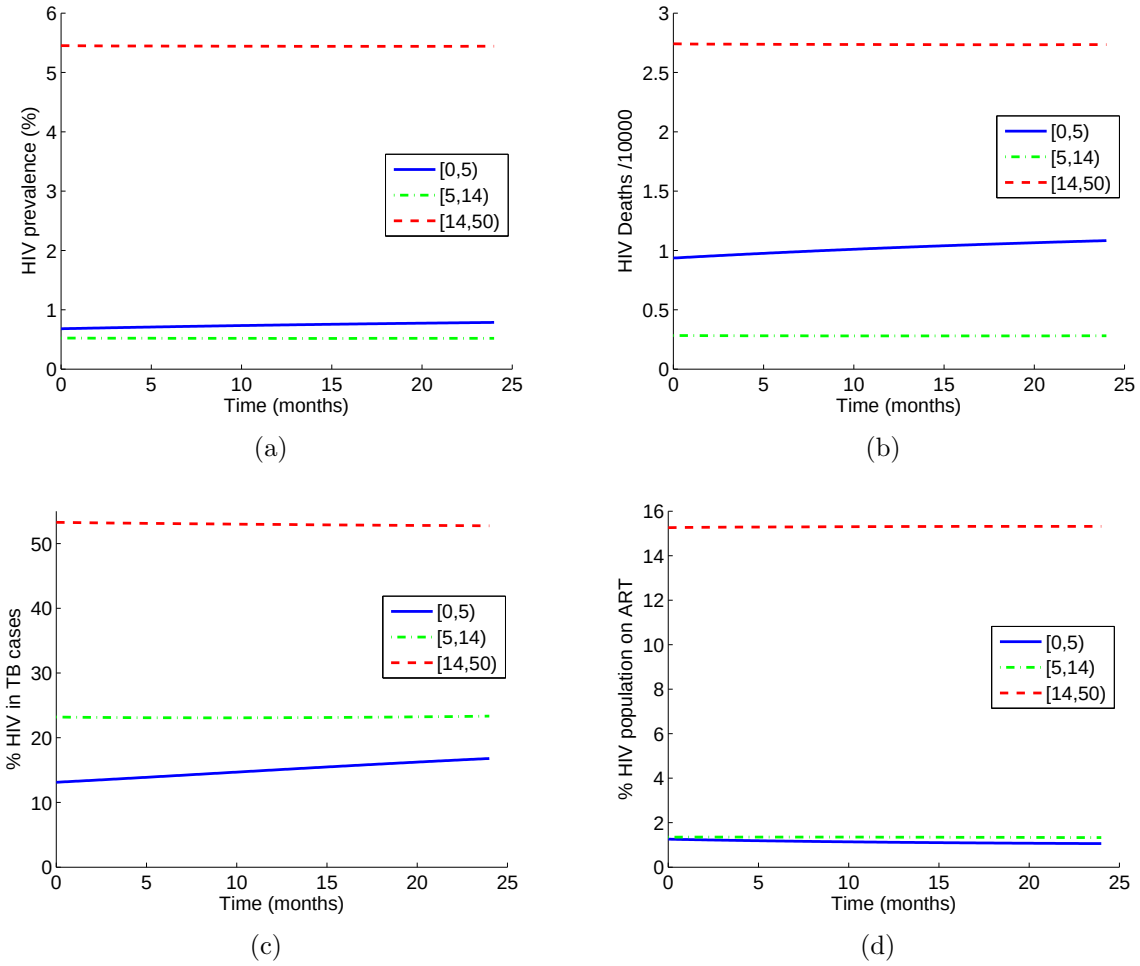


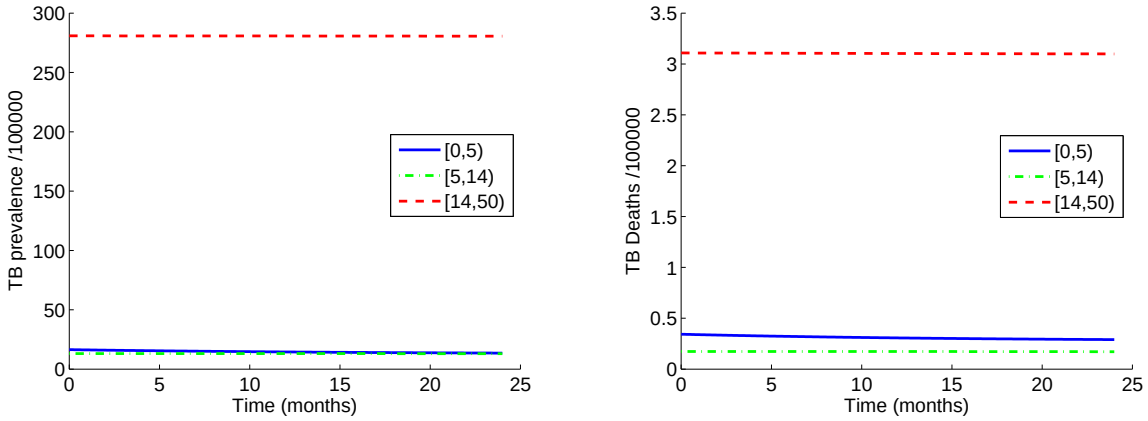
FIG. 5.5. Plots of HIV indicators at baseline

5.6.1 Short term effect of IMID and OSS

In this subsection, we run the model to determine the effect of IMID and combination of IMID and OSS for the period of the intervention.

The cumulative number of HIV positive children at birth decreases with the interventions as displayed by FIG. 5.7(a). On average, the percentage reduction in number of HIV positive children at birth is 0.42 with IMID, 3.3 with IMID+OSS and the incremental percentage reduction by OSS is 2.9 as illustrated in FIG. 5.7(b).

FIG. 5.7(c) shows an increase in the cumulative number of children who acquire HIV through breastfeeding with the interventions as compared to baseline. A percentage in-



(a) (b)

FIG. 5.6. Prevalence of TB in 5.6(a) and TB deaths in Figure. 5.6(b)

crease of 1.5 occurs in that number with IMID and 8.25 with IMID+OSS on average. The incremental increase of OSS is 6.7% and these results are shown in FIG. 5.7(d).

There is a fall in the cumulative number of individuals that get onto ART as illustrated in FIG. 5.8(a) during the period of IMID and the combination of IMID and OSS interventions. The number decreases by 0.037% with IMID and 4.2% with IMID+OSS on average. The reduction due to OSS is 4.2%.

FIG. 5.8(c) demonstrates a very small decrease in the cumulative number of deaths for individuals not on ART. It decreases by 0.0049% with IMID and 0.039% with IMID+OSS. The incremental impact of OSS is a decline of 0.034% as displayed by FIG. 5.8(d).

FIG. 5.9(a) displays a decrease in the cumulative number of TB recovered individuals during the intervention period. In FIG. 5.9(b), this number decreases by 6.9% with IMID and it falls by 5.3% with the combination intervention. The incremental impact of OSS is an increase by 1.63%.

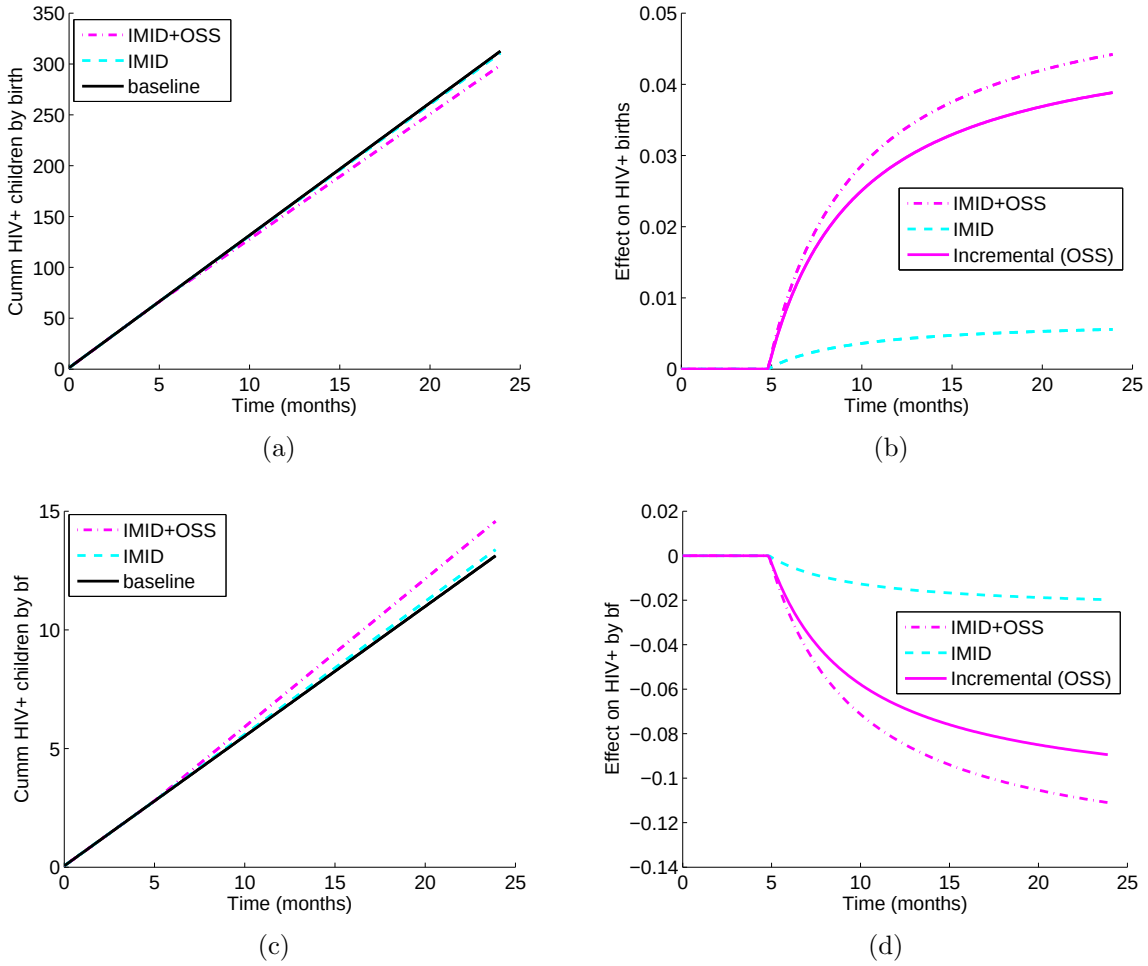


FIG. 5.7. The cumulative numbers of HIV positive children born and the effect of the interventions are shown in FIG. 5.7(a) and FIG. 5.7(b) in turn. FIG. 5.7(c) and FIG. 5.7(d) illustrate the cumulative numbers of children who get HIV infection through breastfeeding and the effect of the interventions for the period of intervention.

5.6.2 Long term effect of IMID and OSS

HIV and TB are diseases that progress on a long time scale. It is thus important that the model is run for a longer period to determine the effect of IMID and the combination of IMID and OSS in the long term.

We simulated the model for an additional five years and the incidence used was extrapolated using the nearest method in Matlab.

We plot averted numbers of HIV infections, deaths and gained numbers of TB recovered

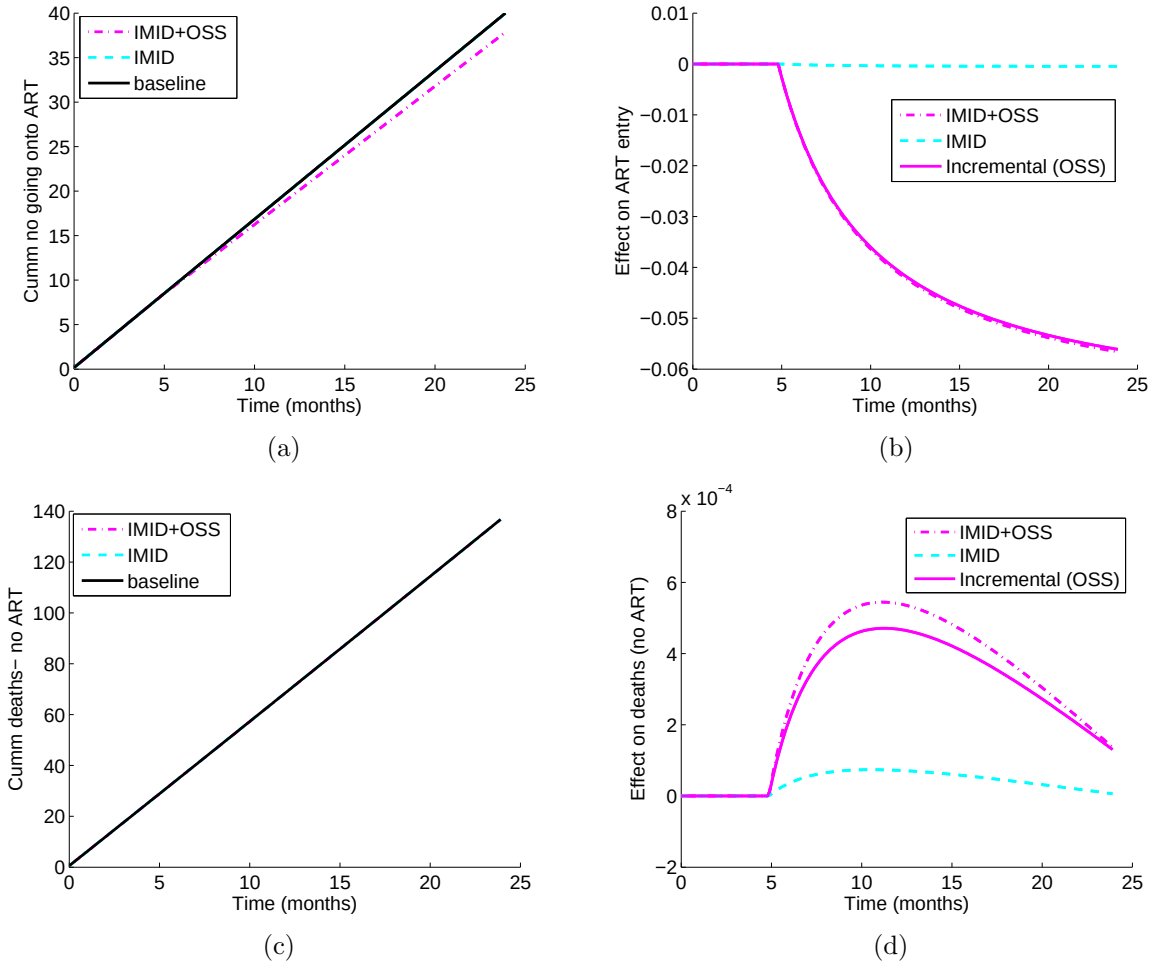
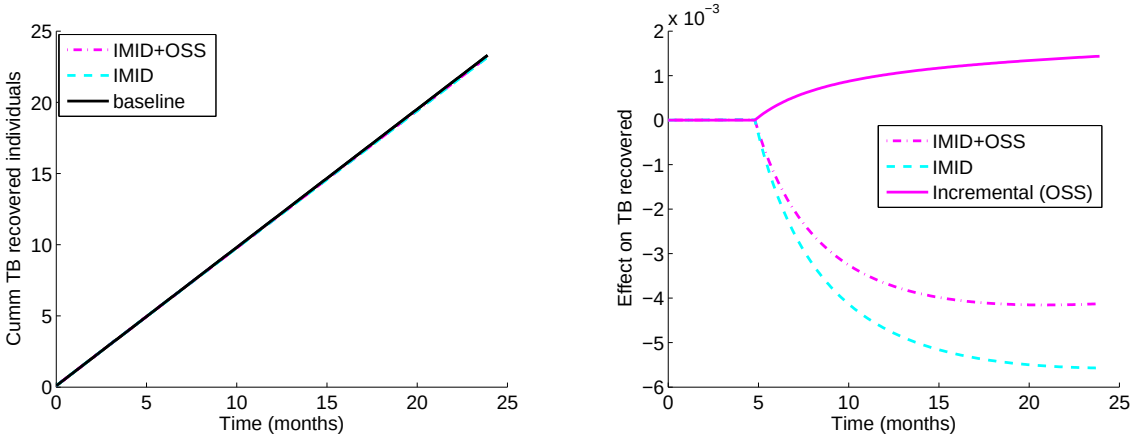


FIG. 5.8. The cumulative numbers of HIV positive individuals recruited onto ART and the cumulative number of deaths in the group with no ART for the period of the interventions are displayed in FIG. 5.8(a) and FIG. 5.8(c). The effect of the interventions on these are given by FIG. 5.8(b) and FIG. 5.8(d).

with the interventions and the effect of the interventions for the additional five years.

Considering number of HIV infections at birth in FIG. 5.10(a), IMID averts about 7, combination of IMID and OSS averts 57 and the incremental infections averted by OSS are 50. The reduction in the number of HIV infections at birth is 0.58% with IMID and 4.58% with IMID and OSS on average and the incremental percentage reduction by OSS is 4.03 in FIG. 5.10(b).

On the other hand, the interventions do not avert any HIV infections that occur through



(a) (b)

FIG. 5.9. FIG. 5.9(a) shows the cumulative number of TB individuals that recover for the period of the intervention. FIG. 5.9(b) gives the effect of the intervention on TB recovered individuals.

breastfeeding, infact the number of HIV infections through breastfeeding increase for the period of the interventions as demonstrated by FIG. 5.10(c). 2 more HIV infections occur during the period of the combination intervention of IMID and OSS.
In FIG. 5.10(d), the cumulative number of children who acquire HIV through breastfeeding increases by 1.98% during period of IMID intervention. During the period of combination intervention, this number rises by 11.1%. The incremental increase during OSS period is 8.95%.

A decline occurs in the cumulative number of individuals that get onto ART. This number reduces by 9 with IMID+OSS and the incremental reduction by OSS is 8 in FIG. 5.11(a). There is a decrease of 0.041% with IMID and 5.8% with IMID and OSS on average. The average reduction for the OSS period is 5.7% as displayed by FIG. 5.11(b).

FIG. 5.11(c) shows a fall in the number of deaths averted for individuals not on ART. On average, the number of deaths averted for individuals not on ART decreases by 0.003% during IMID intervention and 0.032% during the combined intervention. The incremental impact of OSS is a decline of 0.03% as illustrated by FIG. 5.11(d).

In FIG. 5.12(a), the number of TB recovered individuals decreases during the period of the interventions as compared to baseline. This number decreases by 20.2% during IMID and by 11.9% during IMID+OSS. The incremental impact of OSS is an increase by 8.34%.

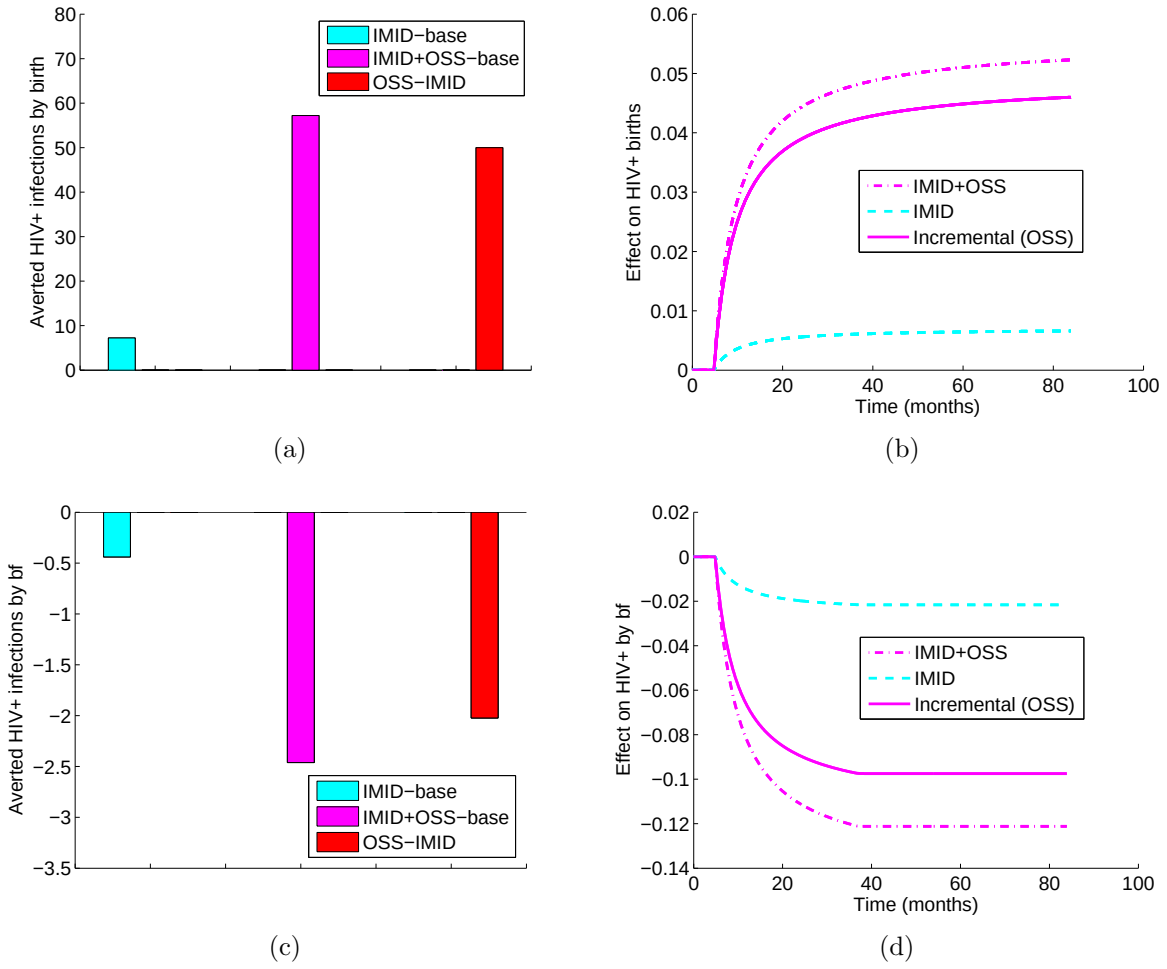


FIG. 5.10. FIG. 5.10(a) and FIG. 5.10(c) display the number of HIV infections that is averted at birth and through breastfeeding. FIG. 5.10(b) and FIG. 5.10(d) show the long term effect of the interventions on the cumulative number of HIV positive children at birth and through breastfeeding respectively.

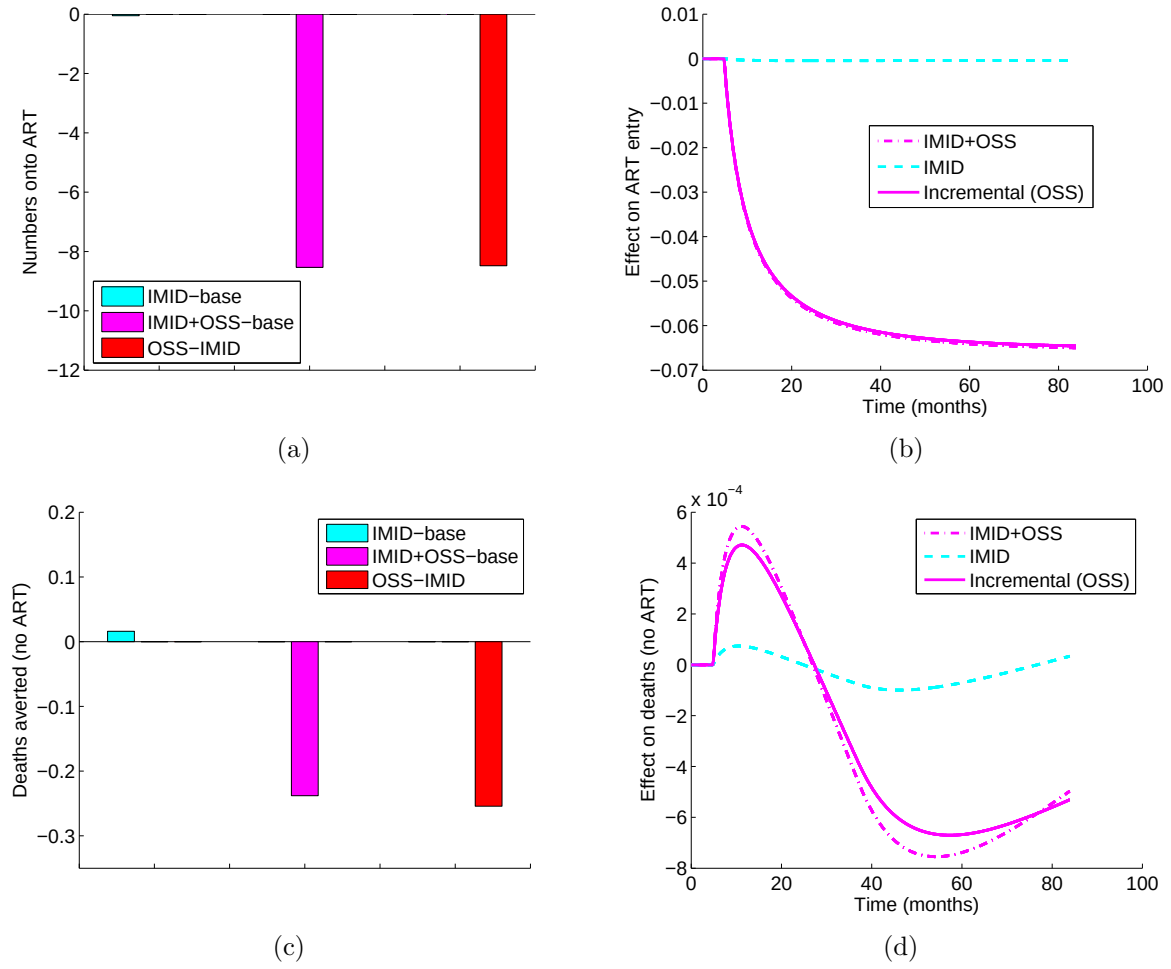
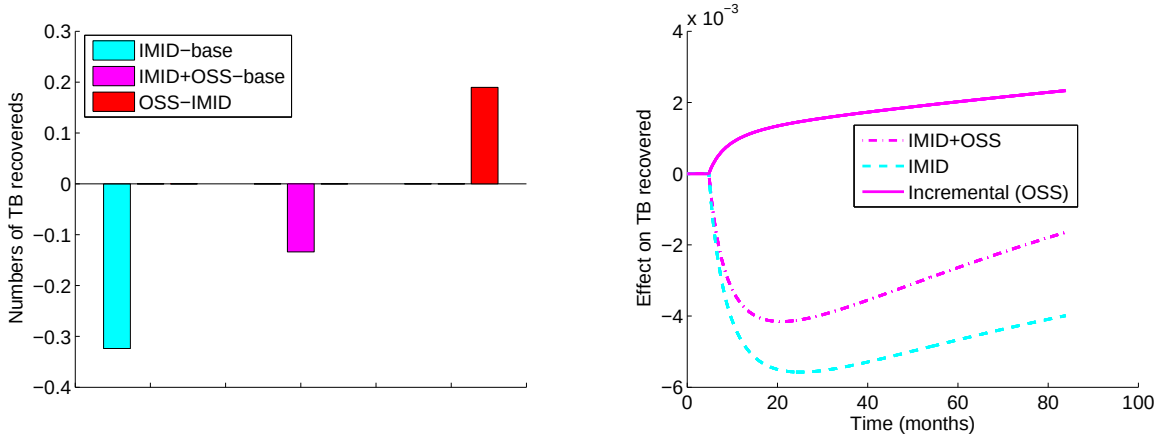


FIG. 5.11. Gained number of individuals that get enrolled onto ART is shown in FIG. 5.11(a) and the number of deaths averted by CTX in group with no ART is given in FIG. 5.11(c). The effect of the intervention of ART enrolment and CTX are shown in FIG. 5.11(b) and FIG. 5.11(d) in turn.



(a) (b)

FIG. 5.12. FIG. 5.12(a) gives the gain in the number of TB recovered individuals with the interventions and FIG. 5.12(b) shows the long term effect of the intervention on TB recovered individuals.

5.7 Discussion

We have explored the impact of IMID and IMID+OSS on HIV and TB in this Chapter for the period of the intervention and an additional period of five years. The results have demonstrated some gains with regards to the interventions in areas such as PMTCT for HIV positive children at birth. However, in some other areas such as ART enrollment, prevention of deaths in individuals not on ART by CTX and TB recoveries, there are little or no gains. Infact, in some cases, the performance was poorer during the interventions as compared to baseline.

HIV positive children The reduction in the cumulative number of HIV positive children at birth can be attributed to the interventions' increase in the testing of HIV positive mothers during IMID+OSS and the increase in the proportion of mothers and infants enrolled into HIV care (refer to TABLE. 3.6). Though the proportion that receive ART for either mothers or HIV exposed children reduces slightly with the interventions, the increase in the testing and enrollment into HIV care proportions cause a positive impact of reducing the number of HIV positive children born as evidenced both in the short term and long term model simulations in FIG. 5.7(a) and FIG. 5.10(a). The results suggest that testing HIV positive mothers and getting them and their infants into HIV care while maintaining (or increasing) the proportion that gets onto ART leads to a reduction in the number of HIV positive births.

On the other hand, the cumulative number of children infected with HIV through breastfeeding increased during the period of the interventions (FIG. 5.7(c) and FIG. 5.10(c)). The reason for this is that the proportion of HIV-exposed children and HIV positive mothers who receive ART on delivery decreased during the IMID and IMID+OSS interventions (refer to TABLE. 3.6).

ART and CTX The cumulative number of HIV infected individuals enrolled onto ART reduced during the intervention period (FIG. 5.8(a) and FIG. 5.11(a)). This is because the proportions of individuals getting onto ART decreased with the interventions (refer to TABLE. 3.6). Though the proportion testing for HIV and enrolling into HIV care

increased, the interventions had no control over drug supplies and stock-outs and as such could do nothing much on getting eligible HIV positive individuals onto ART. This result demonstrates that training for HIV testing, treatment and care needs to be supplemented with availability of drug supplies and equipment as was noted in [155]. Moreover, the proportion of HIV positive individuals on ART in this setting is lower as compared to the national average and this is an already noted concern in some studies [153, 193].

Given that there is almost no change in the proportion of HIV infected individuals that receive CTX during the intervention period, as compared to baseline (refer to TABLE. 3.6), we have the cumulative number of deaths for HIV individuals not on ART decreasing at the start of the interventions (FIG. 5.8(c) and FIG. 5.11(c)) and then increasing soon after that start.
Note that the proportion of HIV positive individuals on CTX is high (≥ 0.9). However, CTX is only accessible to HIV positive individuals who have tested for HIV and have been enrolled into HIV care. The proportion of individuals who take an HIV test (≤ 0.2) and those enrolled into HIV care (≤ 0.6) is small. This implies that the overall proportion of HIV positive individuals on CTX will be small and thus the avertion of HIV deaths by use of CTX will be negligible as suggested by our results.

TB recoveries For the period of the intervention, there is a very small decline in the cumulative number of TB recovered individuals with the interventions as compared to baseline (FIG. 5.9(a) and FIG. 5.12(a)). This is because the proportion of individuals who initiated TB treatment is lower with IMID as compared to baseline where as it is higher for IMID and OSS as compared to baseline (TABLE 3.5).
Note that though the proportion that complete treatment decreases with both interventions and the proportion who initiate treatment falls with IMID, the proportion of individuals who are tested as compared to baseline increases with both interventions (TABLE 3.5) and this accounts for the increase in the cumulative number of TB recovered individuals during the IMID+OSS intervention. This result highlights the importance of testing in management of TB cases.
It is also important to note that the initial proportion of individuals tested for TB is very small which sheds light on the state of the TB management in Uganda, where by individuals are only tested for TB if they have symptoms [170], and there also a number

of delays before patients are initiated on TB treatment [167, 168].

Study limitations There were a number of limitations of the study:

(i) We used the value of the proportion of HIV positive individuals tested as given by the IDCAP data which was the testing proportion considering all outpatients whether positive or negative. We think the testing proportion of HIV positive individuals might be higher than for the general population, but we have no evidence to that thus we used what IDCAP gave. Besides some of the sites were rural and testing proportions are lower there. We assumed a testing proportion of 20% (as given in [40]) that was a higher than the 7.2% for the outpatients but still used the same effect on the proportion of testing as that given in the IDCAP data.

(ii) The effect of ART and PMTCT were not differentiated for pregnant women and we used one average effect putting both of them into consideration.

(iii) For the proportion of HIV positive individuals on ART and on CTX, we considered the proportion that is given for HIV-TB coinfected individuals. This is not so different for other HIV infected individuals such as pregnant women. Moreover, HIV-TB coinfected individual are more likely to get CTX and ART as compared to other groups and HIV pregnant women are fewer in number as compared to HIV-TB coinfected individuals.

(iv) We lacked time series data for HIV and TB cases.

5.8 Summary.

In this section, we have investigated the transmission dynamics of HIV and TB coinfection. We did a mathematical analysis for the sub models and proved the existence and stability of endemic equilibria for both TB and HIV. It was noted that the TB model exhibited a backward bifurcation phenomenon meaning that $R_0^T < 1$ is not sufficient to eradicate the disease.

We then explored the effects of the interventions of IMID and IMID plus OSS for the case management of HIV and TB. HIV testing and TB testing are important in improving quality of health care. We also noted that training alone is not enough and government effort in stocking health centres with drug supplies and equipment is crucial.

Chapter 6

HIV-TB-Malaria-Pneumonia (HTMP) Model

6.1 Introduction

As a continuation of our investigation of the effect of IMID and the combined intervention of IMID and OSS in an integrated way, we formulate a mathematical model that considers all the four diseases: HIV, TB, malaria and pneumonia.

The construction of the HIV-TB-Malaria-Pneumonia (HTMP) model follows from Chapters 4 and 5 that examined the coinfections of malaria and pneumonia and HIV and TB respectively. In addition to those coinfections, we also consider coinfection of HIV and malaria, HIV and pneumonia, TB and malaria, TB and pneumonia and three and more coinfections such as HIV, TB and malaria. However, it is important to note that coinfections with more than two diseases are very rare and mostly occur in severely immunocompromised individuals [104, 108, 110, 190].

6.2 HTMP model

We merge our two models in Chapter 4 and Chapter 5, the model of malaria-pneumonia coinfection with the one of HIV-TB coinfection to form the model with HIV, TB, malaria and pneumonia (HTMP). The coinfections for TB-pneumonia and TB-malaria are rare

and are only considered for model completion.

6.2.1 Model description

The non age structured HTMP model consists of 30 classes. There is a class of susceptible individuals, S. S is made up of individuals that are susceptible to HIV, TB, malaria and pneumonia infections. It also has individuals who are asymptomatic to malaria, pneumonia and latent with TB and these are represented by proportions, m, p and e accordingly.

Infection with HIV represented by λ_H occurs taking individuals to S_1. These get onto ART (at a rate $r_{_H}$) to move to S_2 and they fail ART at a rate $f_{_H}$.
Infection and reinfection with TB (λ_T) occurs for the individuals in the susceptible class sending them to active TB class, I. Individuals with latent TB, a proportion e of susceptible class also reactivate TB infection at a rate ν and move to I. Individual in class I recover at a rate $r_{_T}$. People with active TB may also be infected with HIV to go to I_1 and some of these get onto ART and move to I_2.

In the respective classes of S, S_1, S_2, I, I_1 and I_2, individuals can get infected and reinfected with either malaria ($\lambda_{_{vh}}$) or pneumonia ($\lambda_{_P}$) to progress to symptomatic disease of malaria, M or pneumonia, P. While in the M or P class, people can get infected with pneumonia or malaria in turn to move to malaria-pneumonia coinfection, PM. Symptomatic malaria or pneumonia individuals can develop severe disease at rates $\alpha_{_M}$, $\alpha_{_P}$ and $\alpha_{_{PM}}$ to move to emergency class, $\widetilde{PM}$ and they get out of emergency class at a rate θ. Please note that we have assumed that individuals with malaria and pneumonia do not get infected or reinfected with TB or HIV because malaria and pneumonia are short term duration diseases.

Recruitment occurs by birth and is represented by terms, B and B_1. B is the recruitment for HIV negative people and B_1 accounts for HIV transmission at birth. HIV transmission through breast feeding is represented by $b_{_f}$.
The death rate of individuals is given by μ with a subscript or without. The subscript represents where the death is occurring.

The model diagram is given in FIG. 6.1 and the system of equations are (6.1a)–(6.1e),

(6.2a)–(6.2e), (6.3a)–(6.3e), (6.4a)–(6.4e), (6.5a)–(6.5e),(6.6a)–(6.6e) and (6.7a)–(6.7b).

Please note that the description of the non age structured model is given for purposes of comprehension and we do not use it to obtain any results in this chapter.

The HTMP model with age structure is an extension of the non age structured one. It is divided into three age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$. Individuals age from $[0, 5)$ to $[5, 14)$ at a rate η_1, from $[5, 14)$ to $[14, 50)$ at a rate η_2 and out of $[14, 50)$ at a rate η_3. The parameters in this model are defined similarly as the ones in the model without age structure except that they now have subscript $j = c,\ b,\ a$ representing $[0, 5)$, $[5, 14)$ and $[14, 50)$ age groups respectively. When writing the equations for the age structured model, we code c as equal to 1, $b = 2$ and $a = 3$ such that $j = 1, 2, 3$ stands for $j = c, b, a$ in that order. We do not use $j = 1, 2, 3$ directly because of the some of the parameters and variables we have such as e_1, e_2, p_1, p_2, m_1, m_2, S_1 and S_2 already use the 1 and 2 and need further differentiation with c, b, a to represent which group they are in. The equations of the age structured HTMP model are given in appendix B.

We do not present model diagrams for the age groups, but considering model diagram FIG. 6.1, the one for the $[0, 5)$ age group does not have the HIV transmission term $\lambda_{_H}$ and there is no movement from $I_{_c}$ to $I_{1_{_c}}$. The rest of the in and out flows stay the same.
Model diagram for $[5, 14)$ has no birth terms and no HIV transmission terms but the other flows in and out are the same.
The diagram for $[14, 50)$ has no birth terms, no HIV transmission through breastfeeding but HIV transmission given by $\lambda_{_H}$ and the rest of the flows in and out are the same.

All the model simulations in this chapter are obtained using the age structured model.

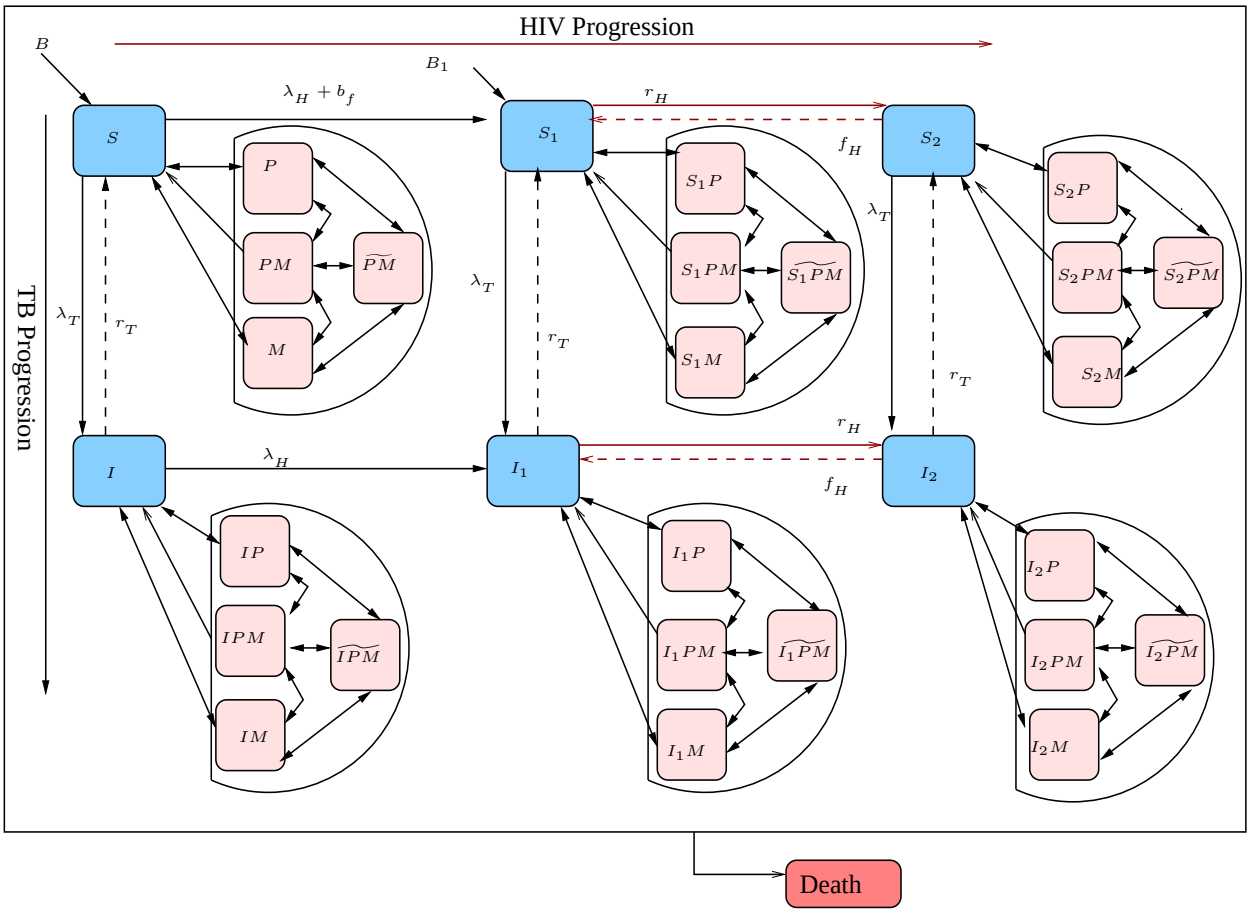


FIG. 6.1. HTMP model diagram

6.2.2 Model equations

Equations for HIV negative individuals

$$\begin{aligned}
\frac{dS}{dt} &= B - b_{_f} + r_{_P}P + r_{_M}M + zr_{_{PM}}PM + r_{_T}I - (\lambda_{_H} + \lambda_{_T}e' + \nu e)S \\
&\quad -(\lambda_{_P}p' + \omega p + \lambda_{_{vh}}m' + \vartheta m + \mu)S, && (6.1a)\\
\frac{dP}{dt} &= (\lambda_{_P}p' + \omega p)S + z_2 r_{_M}PM + \theta q_1\widetilde{PM} - (\lambda_{_{vh}}m' + \vartheta m)P \\
&\quad -(r_{_P} + \alpha_{_P} + \mu_{_P})P, && (6.1b)\\
\frac{dM}{dt} &= (\lambda_{_{vh}}m' + \vartheta m)S + z_1 r_{_P}PM + \theta q_2\widetilde{PM} - (\lambda_{_P}p' + \omega p)M \\
&\quad -(r_{_M} + \alpha_{_M} + \mu_{_M})M, && (6.1c)\\
\frac{dPM}{dt} &= (\lambda_{_{vh}}m' + \vartheta m)P + (\lambda_{_P}p' + \omega p)M + \theta q\widetilde{PM} - zr_{_{PM}}PM \\
&\quad -(z_1 r_{_P} + z_2 r_{_M} + \alpha_{_{PM}} + \mu_{_{PM}})PM, && (6.1d)\\
\frac{d\widetilde{PM}}{dt} &= \alpha_{_P}P + \alpha_{_M}M + \alpha_{_{PM}}PM - (\theta + \mu_{_{\widetilde{PM}}})\widetilde{PM}. && (6.1e)
\end{aligned}$$

$$\begin{aligned}
\frac{dI}{dt} &= (\lambda_{_T}e' + \nu e)S + r_{_P}IP + r_{_M}IM + zr_{_{PM}}IPM - r_{_T}I \\
&\quad -(\lambda_{_H} + \lambda_{_P}p' + \omega p + \lambda_{_{vh}}m' + \vartheta m + \mu_{_I})I, && (6.2a)\\
\frac{dIP}{dt} &= (\lambda_{_P}p' + \omega p)I + z_2 r_{_M}IPM + \theta q_1\widetilde{IPM} - (r_{_P} + \lambda_{_{vh}}m')IP \\
&\quad -(\vartheta m + \alpha_{_{IP}} + \mu_{_{IP}})IP, && (6.2b)\\
\frac{dIM}{dt} &= (\lambda_{_{vh}}m' + \vartheta m)I + z_1 r_{_P}IPM + \theta q_2\widetilde{IPM} - (r_{_M} + \lambda_{_P}p')IM \\
&\quad -(\omega p + \alpha_{_{IM}} + \mu_{_{IM}})IM, && (6.2c)\\
\frac{dIPM}{dt} &= (\lambda_{_{vh}}m' + \vartheta m)IP + (\lambda_{_P}p' + \omega p)IM + \theta q\widetilde{IPM} - zr_{_{PM}}IPM \\
&\quad -(z_2 r_{_M} + z_1 r_{_P} + \alpha_{_{IPM}} + \mu_{_{IPM}})IPM, && (6.2d)\\
\frac{d\widetilde{IPM}}{dt} &= \alpha_{_{IP}}IP + \alpha_{_{IM}}IM + \alpha_{_{IPM}}IPM - (\theta + \mu_{_{\widetilde{IPM}}})\widetilde{IPM}. && (6.2e)
\end{aligned}$$

Equations for HIV positive not on ART

$$\begin{aligned}
\frac{dS_1}{dt} &= B_1 + b_f + \lambda_H S + f_H S_2 + r_{P^1} S_1 P + r_{M^1} S_1 M + z r_{PM} S_1 PM + r_T I_1 \quad (6.3a)\\
&\quad -(\lambda_P p_1' + \omega_1 p + \lambda_{vh} m_1' + \vartheta_1 m + \lambda_T e_1' + \nu_1 e + r_H) S_1\\
&\quad -(\mu_0(1-\gamma p_s) + \mu_1 \gamma p_s) S_1,\\
\frac{dS_1P}{dt} &= (\lambda_P p_1' + \omega_1 p) S_1 + z_2 r_{M^1} S_1 PM + \theta q_1 \widetilde{S_1 PM} - r_{P^1} S_1 P \quad (6.3b)\\
&\quad -(\lambda_{vh} m_1' + \vartheta_1 m + \alpha_{S_1P} + \mu_{S_1P}) S_1 P,\\
\frac{dS_1M}{dt} &= (\lambda_{vh} m_1' + \vartheta_1 m) S_1 + z_1 r_{P^1} S_1 PM + \theta q_2 \widetilde{S_1 PM} - r_{M^1} S_1 M \quad (6.3c)\\
&\quad -(\lambda_P p_1' + \omega_1 p + \alpha_{S_1M} + \mu_{S_1M}) S_1 M,\\
\frac{dS_1PM}{dt} &= (\lambda_{vh} m_1' + \vartheta_1 m) S_1 P + (\lambda_P p_1' + \omega_1 p) S_1 M + \theta q \widetilde{S_1 PM} + z r_{PM} S_1 PM \quad (6.3d)\\
&\quad -(z_1 r_{P^1} + z_2 r_{M^1} + \alpha_{S_1PM} + \mu_{S_1PM}) S_1 PM,\\
\frac{d\widetilde{S_1PM}}{dt} &= \alpha_{S_1P} S_1 P + \alpha_{S_1M} S_1 M + \alpha_{S_1PM} S_1 PM - (\theta + \mu_{\widetilde{S_1PM}}) \widetilde{S_1 PM}. \quad (6.3e)
\end{aligned}$$

$$\begin{aligned}
\frac{dI_1}{dt} &= \lambda_H I + (\lambda_T e_1' + \nu_1 e) S_1 + f_H I_2 + r_{P^1} I_1 P + r_{M^1} I_1 M + z r_{PM} I_1 PM \quad (6.4a)\\
&\quad -(\lambda_P p_1' + \omega_1 p + \lambda_{vh} m_1' + \vartheta_1 m) I_1 - (r_{H_1} + \mu_{I_{1_{c0}}}(1-\gamma p_s)) I_1\\
&\quad -(\mu_{I_{1_{c1}}} \gamma p_s + r_{T_1}) I_1,\\
\frac{dI_1P}{dt} &= (\lambda_P p_1' + \omega_1 p) I_1 + z_2 r_{M^1} I_1 PM + \theta q_1 \widetilde{I_1 PM} - r_{P^1} I_1 P \quad (6.4b)\\
&\quad -(\lambda_{vh} m_1' + \vartheta_1 m + \alpha_{I_1P} + \mu_{I_1P}) I_1 P,\\
\frac{dI_1M}{dt} &= (\lambda_{vh} m_1' + \vartheta_1 m) I_1 + z_1 r_{P^1} I_1 PM + \theta q_2 \widetilde{I_1 PM} - r_{M^1} I_1 M \quad (6.4c)\\
&\quad -(\lambda_P p_1' + \omega_1 p + \alpha_{I_1M} + \mu_{I_1M}) I_1 M,\\
\frac{dI_1PM}{dt} &= (\lambda_{vh} m_1' + \vartheta_1 m) I_1 P + (\lambda_P p_1' + \omega_1 p) I_1 M + \theta q \widetilde{I_1 PM} \quad (6.4d)\\
&\quad -(z r_{PM} + z_1 r_{P^1} + z_2 r_{M^1} + \alpha_{I_1PM} + \mu_{I_1PM}) I_1 PM,\\
\frac{d\widetilde{I_1PM}}{dt} &= \alpha_{I_1P} I_1 P + \alpha_{I_1M} I_1 M + \alpha_{I_1PM} I_1 PM - (\theta + \mu_{\widetilde{I_1PM}}) \widetilde{I_1 PM}. \quad (6.4e)
\end{aligned}$$

Equations for HIV positive on ART

$$\begin{aligned}
\frac{dS_2}{dt} &= r_{_H}S_1 + r_{_{P^2}}S_2P + r_{_{M^2}}S_2M + zr_{_{PM}}S_2PM + r_{_{T_2}}I_2 - f_{_H}S_2 \\
&\quad -(\lambda_{_P}p_2' + \omega_2 p + \lambda_{_{vh}}m_2' + \vartheta_2 m + \lambda_{_T}e_2' + \nu_2 e + \mu_{_{S_2}})S_2, \qquad (6.5a)\\
\frac{dS_2P}{dt} &= (\lambda_{_P}p_2' + \omega_2 p)S_2 + z_2 r_{_{M^2}}S_2PM + \theta q_1\widetilde{S_2PM} - r_{_{P^2}}S_2P \\
&\quad -(\lambda_{_{vh}}m_2' + \vartheta_2 m + \alpha_{_{S_2P}} + \mu_{_{S_2P}})S_2P, \qquad (6.5b)\\
\frac{dS_2M}{dt} &= (\lambda_{_{vh}}m_2' + \vartheta_2 m)S_2 + z_1 r_{_{P^2}}S_2PM + \theta q_2\widetilde{S_2PM} - r_{_{M^2}}S_2M \\
&\quad -(\lambda_{_P}p_2' + \omega_2 + \alpha_{_{S_2M}} + \mu_{_{S_2M}})S_2M, \qquad (6.5c)\\
\frac{dS_2PM}{dt} &= (\lambda_{_{vh}}m_2' + \vartheta_2 m)S_2P + (\lambda_{_P}p_2' + \omega_2)S_2M + \theta q\widetilde{S_2PM} \\
&\quad -(zr_{_{PM}} + z_1 r_{_{M^2}} + z_2 r_{_{P^2}} + \alpha_{_{S_2PM}} + \mu_{_{S_2PM}})S_2PM, \qquad (6.5d)\\
\frac{d\widetilde{S_2PM}}{dt} &= \alpha_{_{S_2P}}S_2P + \alpha_{_{S_2M}}S_2M + \alpha_{_{S_2PM}}S_2PM - (\theta + \mu_{_{\widetilde{S_2PM}}})\widetilde{S_2PM}. \qquad (6.5e)
\end{aligned}$$

$$\begin{aligned}
\frac{dI_2}{dt} &= (\lambda_{_T}e_2' + \nu_2 e)S_2 + r_{_{H_1}}I_1 + r_{_{P^2}}I_2P + r_{_{M^2}}I_2M + zr_{_{PM}}I_2PM \\
&\quad -(r_{_{T_2}} + f_{_H} + \lambda_{_P}p_2' + \omega_2 p + \lambda_{_{vh}}m_2' + \vartheta_2 m + \mu_{_{I_2}})I_2, \qquad (6.6a)\\
\frac{dI_2P}{dt} &= (\lambda_{_P}p_2' + \omega_2 p)I_2 + z_2 r_{_{M^2}}I_2PM + \theta q_1\widetilde{I_2PM} - r_{_{P^2}}I_2P \\
&\quad -(\lambda_{_{vh}}m_2' + \vartheta_2 m + \alpha_{_{I_2P}} + \mu_{_{I_2P}})I_2P, \qquad (6.6b)\\
\frac{dI_2M}{dt} &= (\lambda_{_{vh}}m_2' + \vartheta_2 m)I_2 + z_1 r_{_{P^2}}I_2PM + \theta q_2\widetilde{I_2PM} - r_{_{M^2}}I_2M \\
&\quad -(\lambda_{_P}p_2' + \omega_2 p + \alpha_{_{I_2M}} + \mu_{_{I_2M}})I_2M, \qquad (6.6c)\\
\frac{dI_2PM}{dt} &= (\lambda_{_{vh}}m_2' + \vartheta_2 m)I_2P + (\lambda_{_P}p_2' + \omega_2 p)I_2M + \theta q\widetilde{I_2PM} \\
&\quad -(zr_{_{PM}} + z_1 r_{_{P^2}} + z_2 r_{_{M^2}} + \alpha_{_{I_2PM}} + \mu_{_{I_2PM}})I_2PM, \qquad (6.6d)\\
\frac{d\widetilde{I_2PM}}{dt} &= \alpha_{_{I_2P}}I_2P + \alpha_{_{I_2M}}I_2M + \alpha_{_{I_2PM}}I_2PM - (\theta + \mu_{_{\widetilde{I_2PM}}})\widetilde{I_2PM}. \qquad (6.6e)
\end{aligned}$$

The mosquito dynamics are given by:

$$\begin{aligned}
\frac{dS_v}{dt} &= b_v - (\lambda_{_{hv_c}} + \lambda_{_{hv_b}} + \lambda_{_{hv_a}})S_v - \mu_{_v}S_v, \qquad (6.7a)\\
\frac{dI_v}{dt} &= (\lambda_{_{hv_c}} + \lambda_{_{hv_b}} + \lambda_{_{hv_a}})S_v - \mu_{_v}I_v. \qquad (6.7b)
\end{aligned}$$

Considering the system of equations (6.1a)–(6.1e), (6.2a)–(6.2e), (6.3a)–(6.3e), (6.4a)–(6.4e), (6.5a)–(6.5e),(6.6a)–(6.6e), (6.7a)–(6.7b), we have the following definitions:

$$\begin{aligned} p_1' &= (\gamma p_s p_1 + (1-\gamma p_s)p_0),\ p_1 = (1-p)p_1^1 + pp_2^1,\ p_0 = (1-p)p_1^0 + pp_2^0. \\ m_1' &= (\gamma p_s m_1 + (1-\gamma p_s)m_0),\ m_1 = (1-m)m_1^1 + mm_2^1,\ m_0 = (1-m)m_1^0 + mm_2^0. \\ e_1' &= (\gamma p_s e_1 + (1-\gamma p_s)e_0),\ e_1 = (1-e)e_1^1 + ee_2^1,\ e_0 = (1-e)e_1^0 + ee_2^0. \end{aligned}$$

where:

(i) 0 represents not on CTX and 1 represents being on CTX for the respective asymptomatic and symptomatic classes.
p_1^0, m_1^0, e_1^0 are the proportions of new infections that become symptomatic for HIV infected individuals not on CTX for pneumonia, malaria and TB respectively.
p_1^1, m_1^1, e_1^1 are the proportions of new infections that become symptomatic for HIV infected individuals on CTX for pneumonia, malaria and TB accordingly.

(ii) p_2^0, m_2^0, e_2^0 are the proportions of reinfections that become symptomatic for HIV infected individuals not on CTX for pneumonia, malaria and TB respectively.
p_2^1, m_2^1, e_2^1 are the proportions of reinfections that become symptomatic for HIV infected individuals on CTX for pneumonia, malaria and TB in turn.

(iii) $\lambda_{_H} = \beta_{_H} I_H/N$. $\beta_{_H}$ is the infection rate for HIV. I_H is the HIV infected human population and N is the total human population.

(iv) $\lambda_{_T} = (\beta_{_T} I_{_T} + \beta_{_{TH}} I_{_{TH}})/N$. $\beta_{_T}$ is the rate at which HIV negative active TB individuals pass on infection and $\beta_{_{TH}}$ at which coinfected HIV-TB individuals transmit the TB infection.

(v) $\lambda_{_{vh}} = \beta_{_{vh}} I_v/N$. $\beta_{_{vh}}$ is the rate at which a vector (mosquito) infects a human, I_v is the infected vector (mosquito) population and N is the human population.

(vi) $\lambda_{_{hv}} = \beta_{_{hv}}(I_{_M}/N)$, $\beta_{_{hv}}$ is the rate at which a vector (mosquito) becomes infected by biting an infected human and I_M is the human population infected with malaria and it is made up of all the malaria individuals including those with asymptomatic malaria infection.

(vii) $\lambda_P = \beta_p I_P/N$. β_p is the infection rate for pneumonia. I_P is the infected pneumonia population and it is made up of all the pneumonia individuals including those with asymptomatic pneumonia infection.

6.3 Coinfections

This section deals with the other coinfections that have not been studied in detail. It is important to note that the prescence of HIV infection plays an important role in the occurrence of coinfections. We consider the effect of coinfections on infection, recovery, mortality and morbidity of patients and the effect of treatment such as ART and CTX when administered to coinfected patients.

6.3.1 HIV-malaria coinfection

HIV increases the risk of malaria infection and the development of clinical malaria, both uncomplicated and severe [1, 72, 83, 104, 174]. HIV and malaria coinfection was associated with clinical episodes of malaria in a Ugandan study [63] and increase in malarial fever was noted with advanced HIV infection [72].

The increase in infection rates and malarial fevers in HIV individuals coinfected with malaria is approximately 2-fold when compared to HIV infected individuals without malaria. There is also evidence of increased viral load if an HIV infected individual has malaria [15].

ART and CTX use reduce the incidence of malaria in HIV positive individuals [36, 121, 163]. The reduction of malaria incidence by CTX ranges between 30% to 82% [121, 194] and that of ART ranges from 40% to 93% [121].

6.3.2 HIV-pneumonia coinfection

HIV infection is considered a risk factor for pneumonia both in adults and children [70, 113]. The most causative agent is *S. pneumoniae* whose colonisation is increased by HIV infection [70, 113, 209]. Other causative agents include Staphylococcus aureus and Gram-negative

bacteria and Pneumocystis jirovecii (PCP) [68, 70]. In a Ugandan study, the prevalence of oropharyngeal colonization with pneumococci was 18% in HIV infected patients [22].

Incidence of pneumonia is higher in HIV infected individuals than in HIV uninfected individuals [56, 173, 181, 182] and it increases with falling CD4 cell count [56, 78, 136]. The risk of invasive disease due to *S. pneumoniae* was estimated to be 40 times more in HIV infected children than HIV negative children [68] and about 25 times higher in HIV infected adults than HIV negative ones [56].
The rate of pneumonia episodes was 0.055 per year for HIV positive and 0.009 for HIV negative [78]. The rates of pneumonia per year ranged from 0.023 to 0.108 for CD4 cell count of $> 500/mm^3$ to $< 200/mm^3$ and the rate was 0.02 per year for HIV negative individuals [78, 136].

Mortality due to pneumonia is higher in HIV positive individuals than in uninfected people [173, 182]. There is a three to six fold increase in mortality for HIV infected individuals with pneumonia than those that do not have it [182, 209]. The case fatality rate for acute pneumonia in HIV infected children is 3 to 6 times more than that for HIV negative children [68].

Increased access to ART has lead to a decrease in pneumonia morbidity and mortality [70, 113, 182]. A decrease in the range 0.0082 to 0.016 rate of pneumonia in AIDS patients per year in the pre-HAART era to the range 0.0019 to 0.0042 after the introduction of HAART occurred. This is about 4 times reduction in rate of pneumonia with ART. Incidence of pneumonia requiring hospitalization reduced from 1.4 to a range 0.035 to 0.08 because of HAART. Bacteremia incident episodes decreased from 0.0118 in the pre HAART era to a range 0.005 to 0.0063 in the post HAART era [136].
CTX also reduces the morbidity with pneumonia by 65% in HIV positive individuals eligible for ART [123, 131, 208].

6.3.3 TB-malaria or TB-pneumonia

TB coinfection with malaria is very rare and has very little documention. TB coinfection with pneumonia is also rare but there are a few case studies that have looked at individuals with both TB and pneumonia [130, 169]. It is important to note that these individuals

had other infections such as Influenza and HIV. This highlights the role that HIV plays in coinfections.

6.3.4 Three or more coinfections

These are rare but can occur in very immunocompromised patients. With HIV infection, it is relatively common for infected individuals to have mixed pulmonary infections. Some studies looked at HIV infected individuals with HIV, TB and pneumonia [110, 165]. In [133], a study to characterize the coinfections of HIV with TB and malaria was done. HIV-malaria and HIV-TB-malaria were the least prevalent. HIV-TB coinfection was the most deadliest, followed by HIV-TB-malaria. In [164], some of the HIV infected children with culture positive TB also had pneumonia.
There is very limited literature on the effects of three or more coinfections and for this reason, we will refer to HIV and its effect when part of a coinfection and the rest of the effects will be assumed.

6.4 Parameters of the HTMP model

Most of the parameters used in the numerical simulations for this model remain the same as those in Chapters 3 and 4 except for the progression to disease proportions, reactivation rates and mortality rates.

Even though there is evidence suggesting that HIV positive individuals are more susceptible to malaria infection [77, 92, 195] and more colonisation by *S. pneumoniae* [70, 113, 209], we do not differentiate the infection rate between HIV positive and HIV negative individuals. However, we consider that the proportions that develop disease after infection and reinfection and those that reactivate to disease are higher for HIV positive individuals than for HIV negative individuals.

We assume that the reactivation rate for HIV positive individuals is increased by 6 times for both HIV coinfected individuals with malaria and pneumonia and the proportions that progress to disease are increased by 4 times.

ART reduces the reactivation rates and proportions that progress to disease by 50% and CTX reduces these rates and proportions by 40% [36, 121, 163, 194]. Note that higher reductions by ART and CTX consider individuals who are eligible for ART but for our case we consider the average for all the HIV positive individuals and thus we use an a lower percentage reduction.

Mortality is increased by 6 times for HIV individuals coinfected with pneumonia as compared to HIV positive individuals without pneumonia [182, 209].
For mortality in HIV-malaria coinfected individuals, we assume that it is 5 times that of HIV positive individuals without malaria. Please note that though there are documentations about the higher risks in mortality, morbidity for HIV-malaria coinfected individuals, concrete values about how much being HIV positive increases one's mortality or morbidity rates are not given [77, 92, 195].

There is conflicting evidence about recovery from malaria in HIV-malaria coinfected individuals [77]. However, in a study carried out in Uganda [92], results suggested that HIV-malaria coinfected individuals had a lower recovery rate than those that had HIV only. Nevertheless, for our model simulations, we did not differentiate the recovery rates between HIV positive and HIV negative individuals.

This model has very many parameters and in some instances, we considered some of the parameters to be constant for both HIV positive and HIV negative individuals if it was within reason, for example, the recovery rates. Also note that though some literature exists on HIV coinfections, it is mostly comparison between HIV negative and HIV positive individuals and not necessarily a comparison between HIV positive and HIV-coinfected.

6.5 Model simulations

In this section, we simulate the age-structured HTMP model given by equations in appendix B. We run simulations for baseline and those for the effect of IMID and combination of IMID and OSS. However we need to take note of some of the mathematical challenges that this model faces

6.5.1 Numerical challenges

Please note that the HTMP model has two different time scales and this presents numerical challenges. Malaria and pneumonia occur in the order of days while HIV and TB dynamics are in order of years. In such cases, the steady-state approximation is used (as was done in [107]) and this leads to the formation of differential algebraic equations. These are stiff ODEs and are solved by using non-standard numerical methods. However, Matlab software can solve differential algebraic equations of index 1 [171].
The steady-state approximation is generalised by the slow manifold theory and the singular perturbation theory [25]. The slow manifold theory is such that the curves and surfaces that arise from the steady-state approximation can be understood as approximations to slow invariant manifolds of the differential equations.
On the other hand, the singular perturbation theory is such that a small parameter that multiplies a derivative is considered.

For our case, we did not consider a steady-state approximation for malaria and pneumonia because we had to use the change in mosquito dynamics to fit the malaria data that we have. Thus, we used an intermediate time scale of months for malaria, pneumonia, HIV and TB. This solved the stiffness problem and gave reasonable results. Besides, the interventions were evaluated in period of months and not days or years.

6.5.2 Baseline graphs

The HTMP model is calibrated to have a similar baseline to that of malaria-pneumonia coinfection and HIV-TB coinfection models. FIG. 6.2(a), FIG. 6.2(b), FIG. 6.2(c) and FIG. 6.2(d) show baseline HIV and TB prevalence, malaria and pneumonia cases respectively.

FIG. 6.3(a), FIG. 6.3(b), FIG. 6.3(c) and FIG. 6.3(d) also show the proportion of TB diseased individuals with HIV, proportion of HIV individuals with malaria, proportion of HIV individuals with pneumonia and proportion of pneumonia individuals with TB.

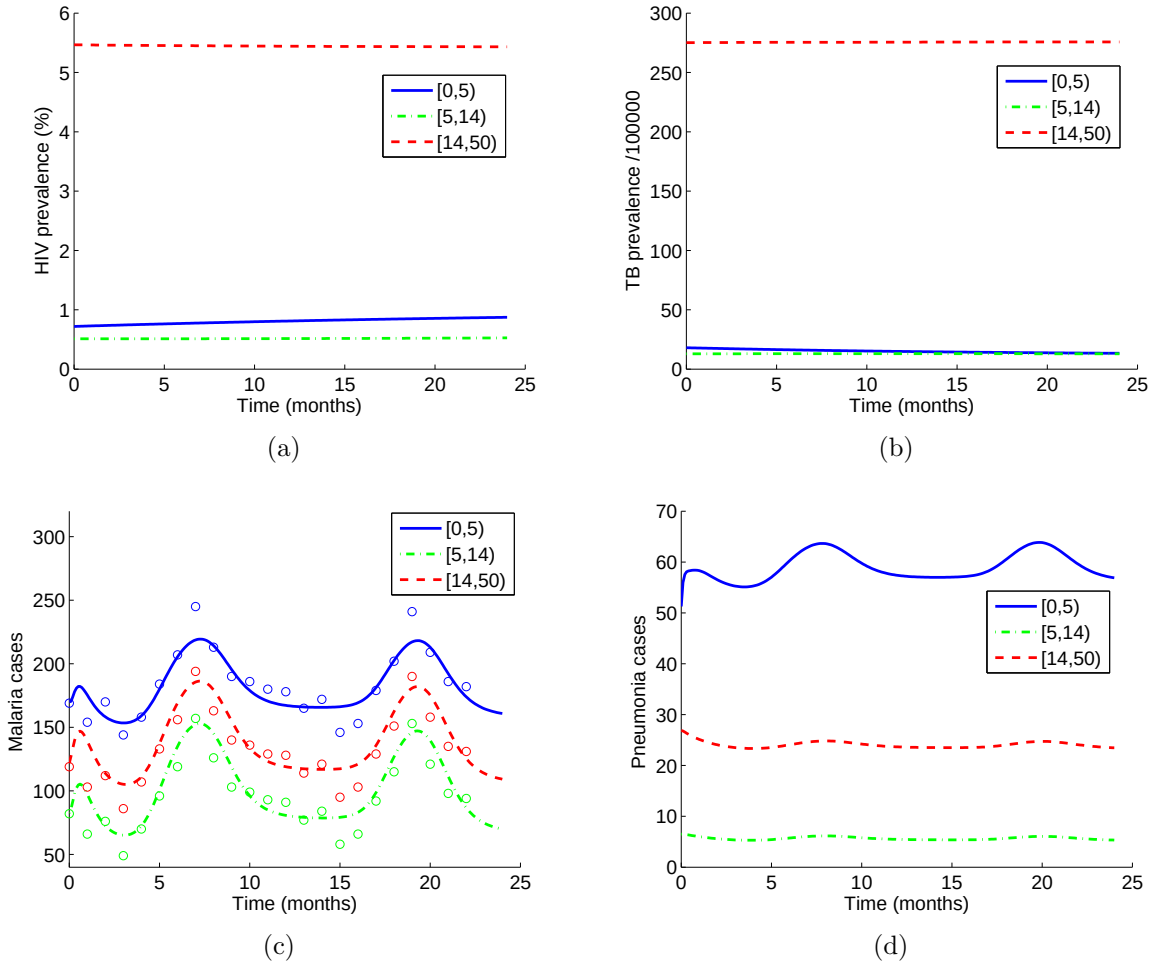


FIG. 6.2. Baseline indicators for HIV, TB, malaria and pneumonia.

6.5.3 Effect of IMID and OSS

In this subsection we run simulations of the cumulative number of deaths in HIV, TB, malaria and pneumonia and estimate the effect of IMID and combined intervention of IMID and OSS on these.

The cumulative number of malaria deaths decreases with the two interventions as shown in FIG. 6.4(a). During the period of IMID, this number decreases by about 5 deaths and it decreases by 32 deaths during the combined intervention of IMID and OSS. The percentage reduction by IMID is 4.0, that of the combined intervention is 24.6 and the incremental percentage reduction is 21.5 on average. This is displayed by FIG. 6.4(b).

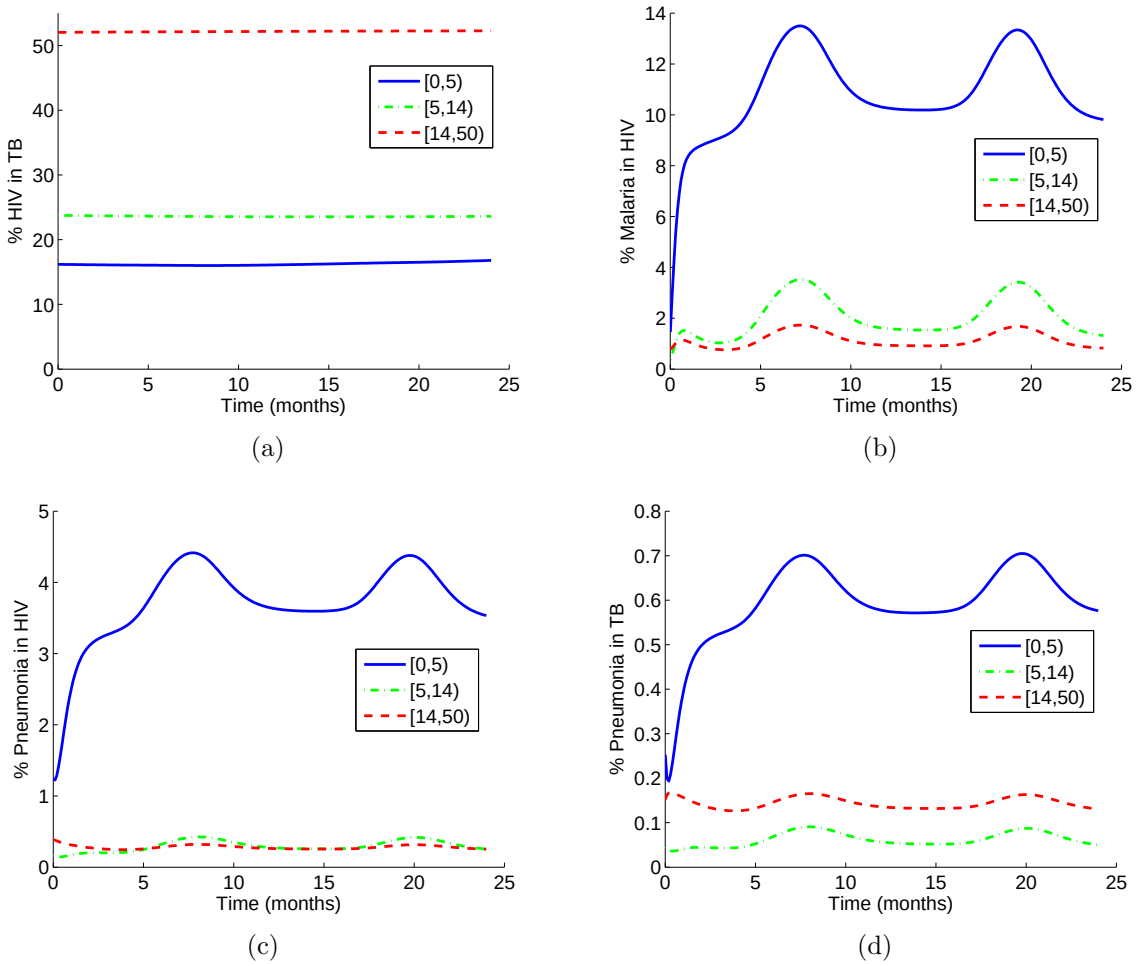


FIG. 6.3. Proportions of coinfection disease

FIG. 6.4(c) shows that IMID and IMID+OSS lead to a fall in the cumulative number of pneumonia deaths. On average, this number is reduced by 14 deaths for IMID, 64 deaths by IMID+OSS. The mean reduction by IMID on the number of deaths is 4.1%, that of IMID+OSS is 18.7% and the added reduction by OSS alone is 15.3%.

FIG. 6.5(a) shows a decrease in the cumulative number of HIV deaths with the interventions. In FIG. 6.5(b), the number of HIV deaths is reduced by 0.085% during IMID period and it declines by 0.47% for IMID+OSS. The incremental decrease by OSS is 0.39%.

FIG. 6.5(c) displays a decline in the cumulative TB deaths for the duration of the interventions. The results in FIG. 6.5(d) give the estimated reduction by IMID as 0.11% on average, that by IMID+OSS as 0.35% and that by OSS alone as 0.23%.

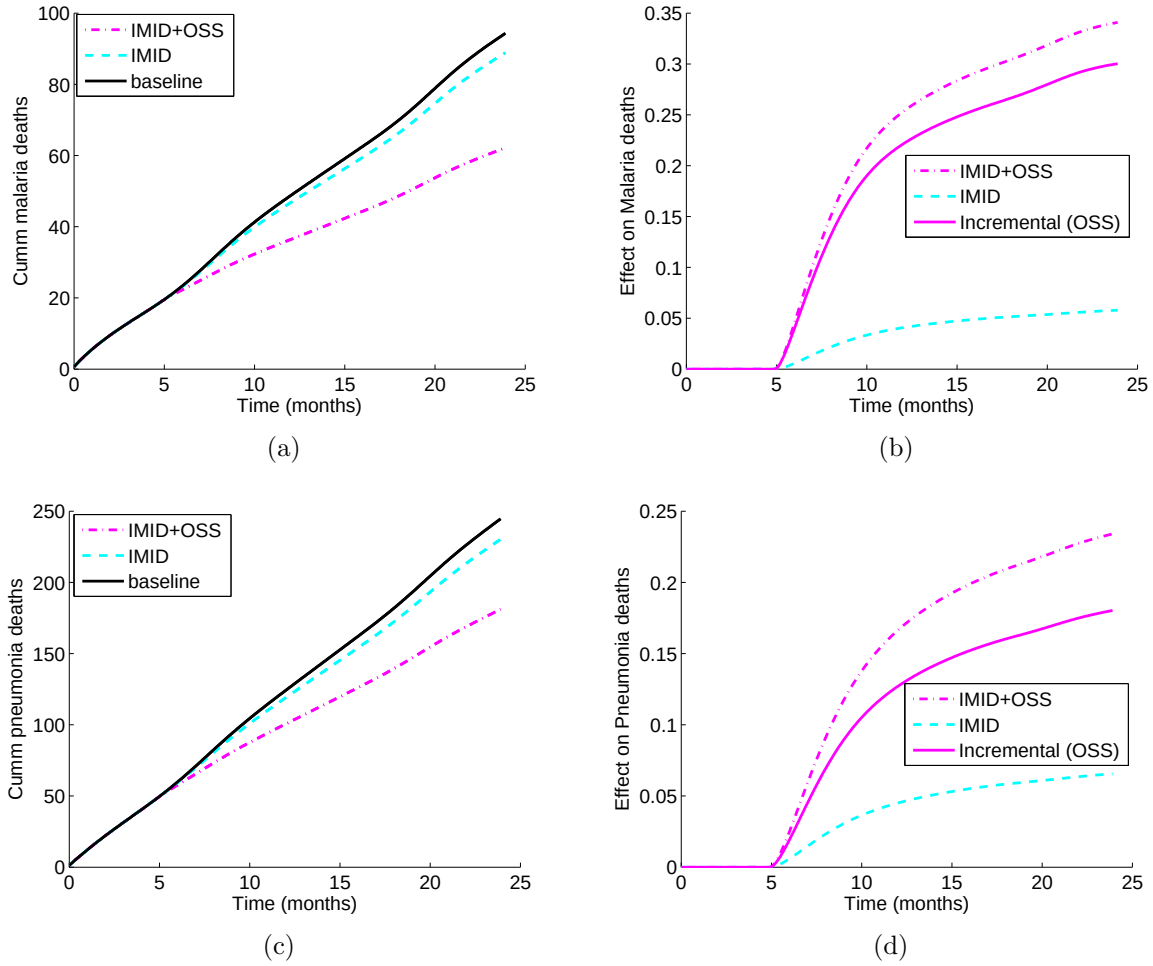


FIG. 6.4. Cumulative numbers of deaths in malaria and pneumonia and the effect of IMID and OSS on malaria deaths and pneumonia deaths

The cumulative number of TB recovered individuals decreases during the period of the interventions as demonstrated by in FIG. 6.9(c). The percentage increase by IMID is 0.43, that of IMID and OSS is 0.21% and the added percentage increase by OSS is 0.22

In FIG. 6.6(a), the cumulative number of individuals going onto ART decreases with the two interventions with the fall being more with the combined intervention of IMID and OSS. There is about 1 individual less going onto ART for IMID+OSS. In FIG. 6.6(b), the percentage decrease by IMID is 0.013%, that of the combined intervention is 3.9% and the incremental reduction by OSS is 3.9%.

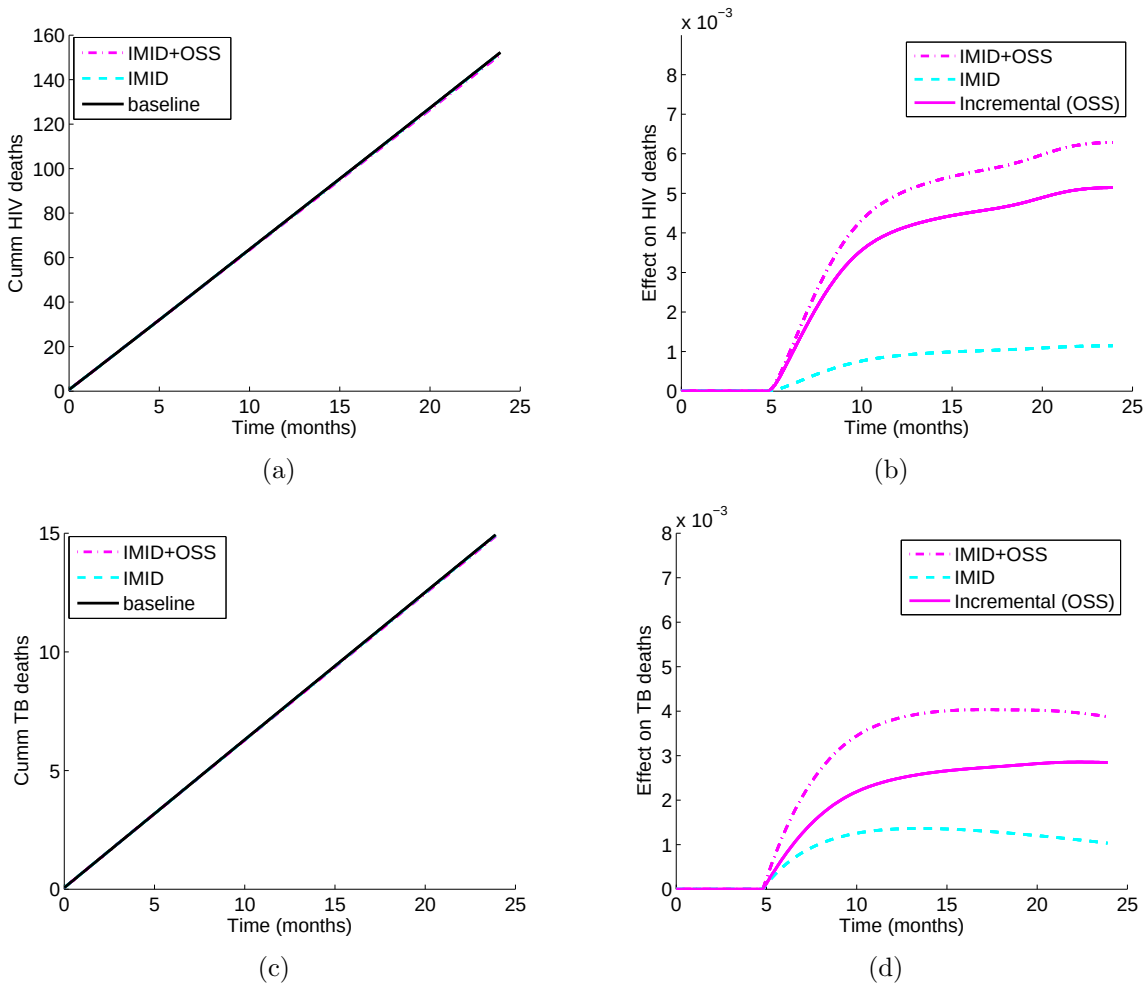


FIG. 6.5. Cumulative numbers of deaths in HIV and TB and the effect of IMID and OSS on HIV deaths and TB deaths

6.5.4 Investigating Scenarios

We then consider an hypothetical situation of having 25% effect by IMID on the indicators followed by 25% effect by IMID+OSS on the indicators, with 100% coverage for the period of the intervention.

Since the performance indicators (TABLE. 3.4 and TABLE. 3.5) are given in terms of proportions, we make sure that they do not go beyond 1. Thus the only proportions that get a 25% effect by IMID, followed by 25% effect by OSS are those ≤ 0.64.
For those greater than 0.64 but ≤ 0.79, we apply the 25% effect by IMID, followed by an effect of OSS that results into a proportion of 1.

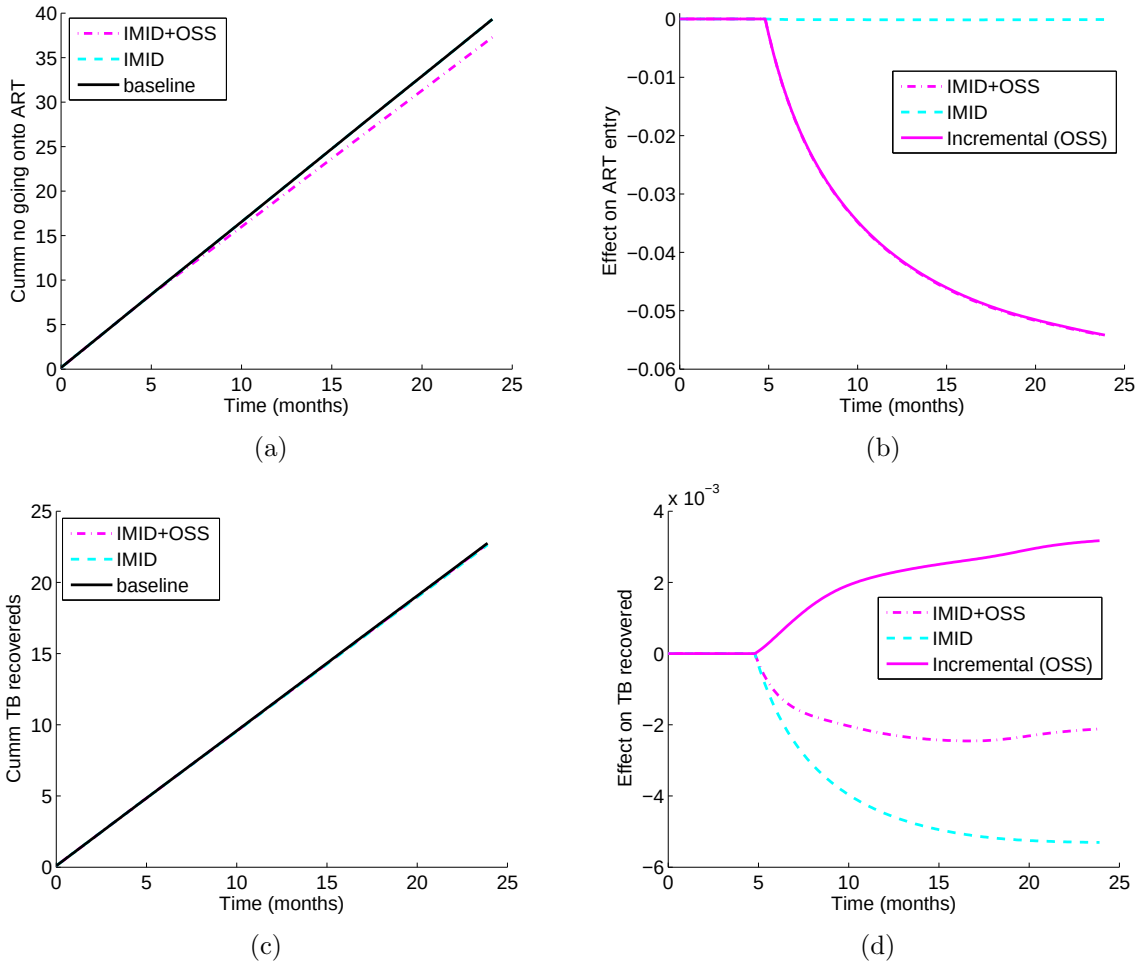


FIG. 6.6. Cumulative numbers of individuals enrolled onto ART, TB recovered individuals in FIG. 6.6(a) and FIG. 6.6(c). The effects of IMID, IMID and OSS and the incremental impacts of OSS are shown in in FIG. 6.6(b) and in FIG. 6.6(c) respectively.

For those greater than 0.79, we only apply the effect by IMID that takes them to a proportion of 1 and no effect by OSS.

With the baseline as the reference, the proportions that are ≤ 0.64 will have a 25% effect by IMID and 56.3% effect by IMID+OSS.

For our numerical simulations, we consider the number of deaths averted for malaria, pneumonia, HIV and TB. We also run simulations for gains in number of individuals that go onto ART and gain in number of TB recovered individuals with the interventions.

The number of malaria deaths decreases with the two interventions as shown in FIG.

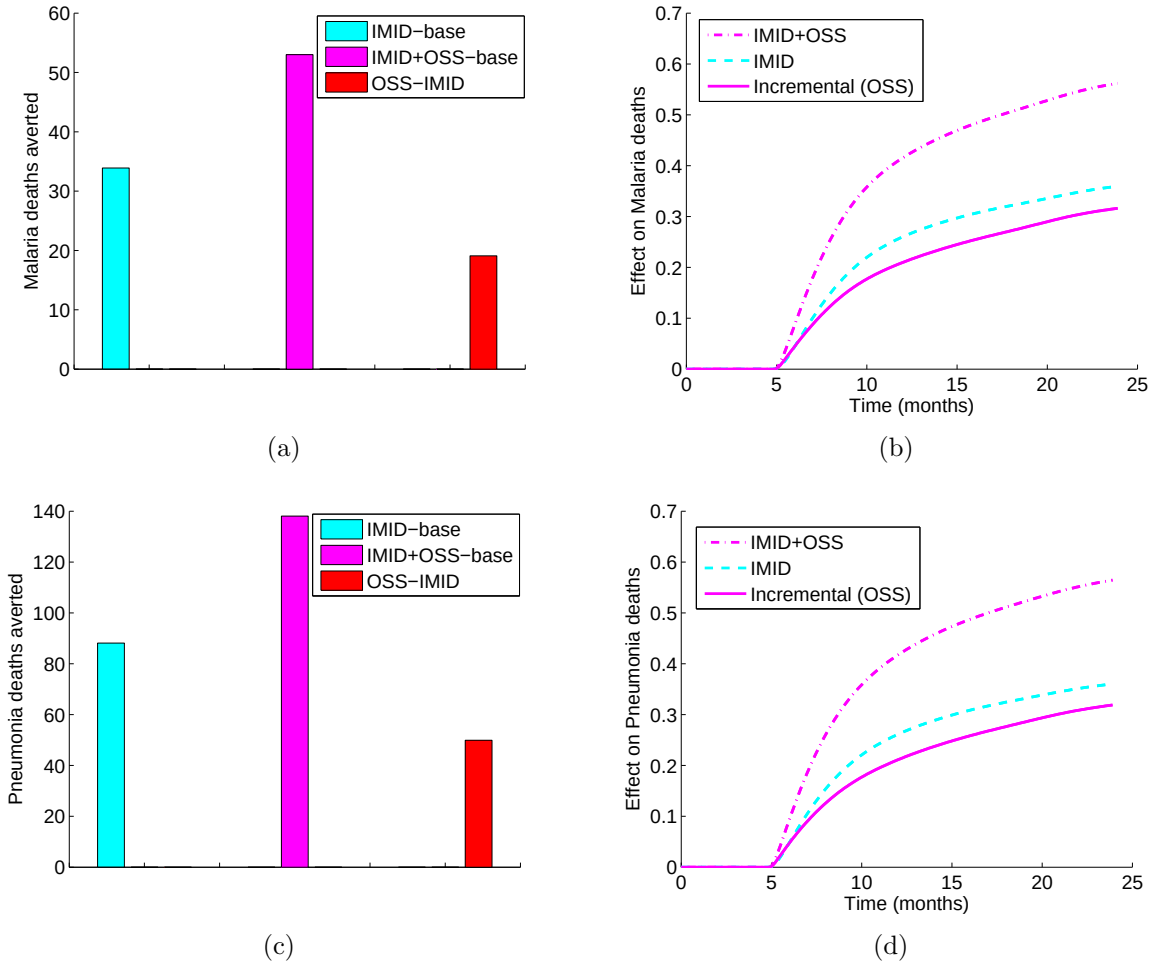


FIG. 6.7. Averted deaths for malaria and pneumonia with the interventions in FIG. 6.7(a) and FIG. 6.7(c). FIG. 6.7(b) and FIG. 6.7(d) given the effects of the two interventions on malaria and pneumonia deaths respectively.

6.7(a). It decreases by 34 deaths with IMID, 53 deaths with IMID+OSS and 19 deaths with OSS only. On average, the percentage reduction by IMID is 25.6, that of the combined intervention is 40.8 and the incremental percentage reduction is 21.6 as displayed by FIG. 6.7(b).

FIG. 6.7(c) shows that IMID and IMID+OSS lead to a fall in the number of pneumonia deaths. IMID averts 88 deaths, combined intervention averts 138 deaths and OSS only averts 50 deaths. IMID decreases the number of pneumonia deaths by 25.8%, IMID+OSS reduces it by 41% and the reduction by OSS only is 21.8%.

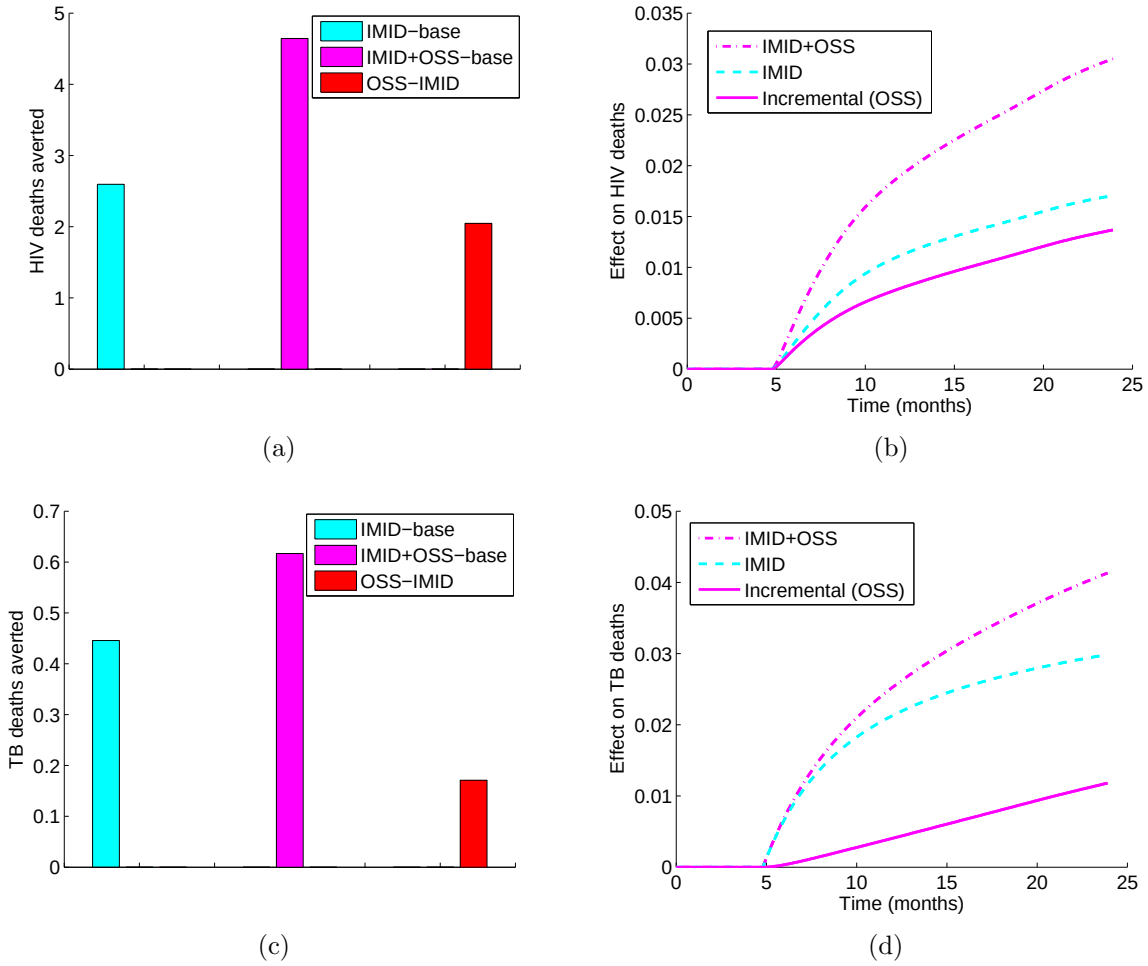


FIG. 6.8. HIV and TB deaths averted with the interventions of IMID and IMID plus OSS in FIG. 6.8(a) and FIG. 6.8(c). The effects of IMID and OSS on HIV deaths and TB deaths are shown in FIG. 6.8(b) and FIG. 6.8(d)

On average, 3 HIV deaths are averted during IMID, 5 deaths are averted during IMID+OSS and 2 deaths are averted by OSS only as shown in FIG. 6.8(a). The average effect of IMID on HIV deaths is a reduction of 1.2%, that by IMID+OSS is 2.0% and the incremental decrease by OSS only is 0.87%.

FIG. 6.8(c) shows that IMID and OSS averts one TB death but with most of this being as a result of IMID and not OSS. The estimated mean reduction by IMID is 2.2%, that by IMID and OSS is 2.7% and the incremental decrease by OSS is 0.57%.

In FIG. 6.9(a), 1 more individual is enrolled onto ART by IMID+OSS intervention as

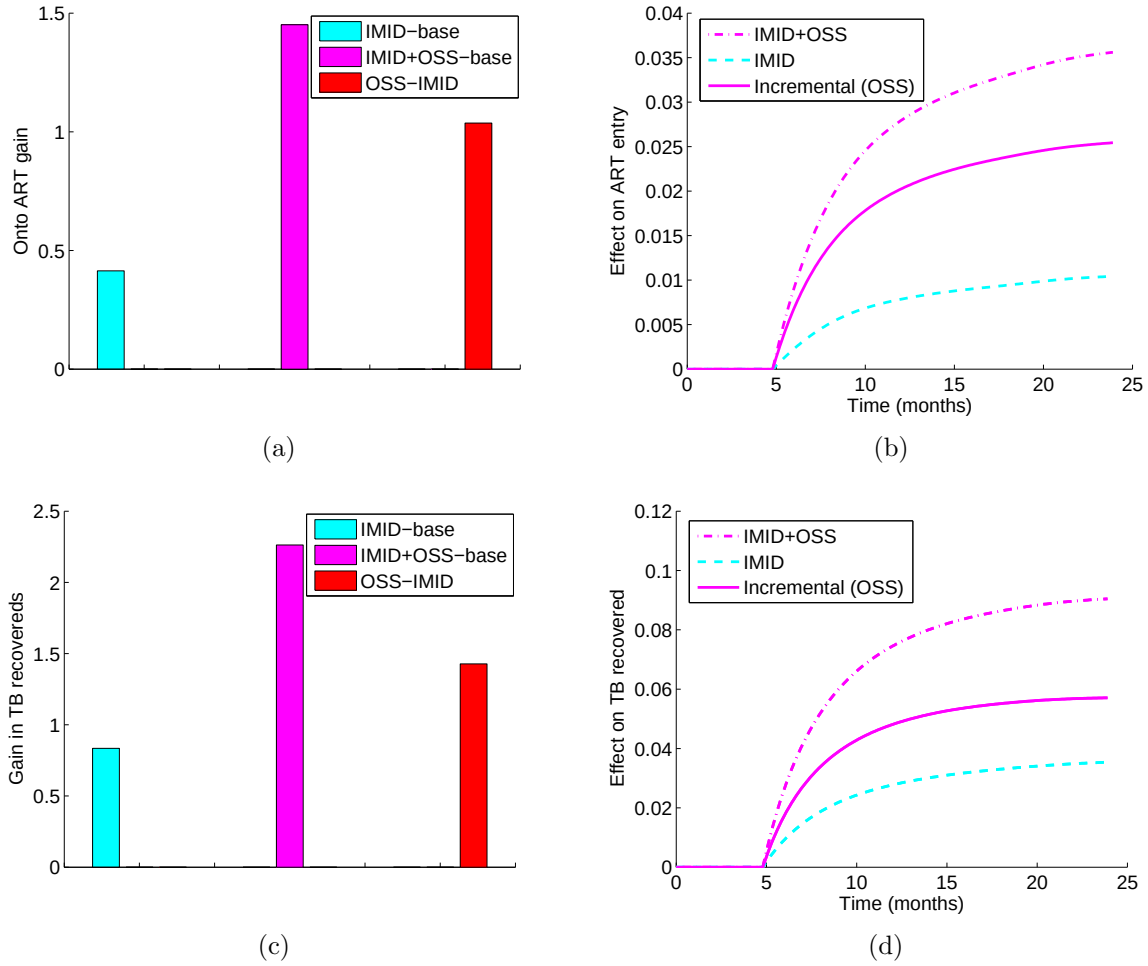


FIG. 6.9. Cumulative numbers of individuals enrolled onto ART, TB recovered individuals in FIG. 6.9(a) and FIG. 6.9(c). The effects of IMID, IMID and OSS and the incremental impacts of OSS are shown in in FIG. 6.9(b) and in FIG. 6.9(c) respectively.

compared to baseline. OSS contributes more for ART enrollment. The effect of IMID is an increase of 1.7%, that for IMID and OSS is 2.7% and the incremental impact by OSS is an increase by 1.98% as shown in FIG. 6.9(b).

The number of TB recovered individuals increases by 1 with IMID as compared to baseline and by 2 with the combined intervention as compared to baseline in FIG. 6.9(c). The percentage increase by IMID is 2.7, that of IMID and OSS is 7.2% and the added percentage increase by OSS is 4.6

6.6 Discussion

We have explored the effect of IMID and OSS on HIV, TB, malaria and pneumonia using an integrated infectious diseases model that we developed. We have simulated the model with the actual effects of IMID and combination intervention of IMID and OSS to investigate the effect of the interventions on the cumulative number of deaths resulting from the four diseases, the cumulative number of individuals who are enrolled onto ART, and the cumulative number of individuals who recover from TB. We also investigated a scenario of having a 25% effect of IMID followed by a 25% effect of IMID+OSS on performance indicators with 100% coverage, and simulated results.

Malaria and pneumonia Considering results for malaria and pneumonia, it is clear that the two interventions are effective in reducing the number of deaths.
Increasing the coverage and effect of the two interventions leads to more reduction in the number of deaths as demonstrated by the hypothetical situation. This reduction as discussed in Chapter 3 is due to the improvement in the performance indicators (TABLE 3.4) by the two interventions.
OSS performs better than IMID with the actual effects on the indicators as well as with the hypothetical situation. This is as expected because practical training should add value to classroom training.

HIV and TB The interventions reduce the number of HIV deaths with more reduction noted with the combined intervention of IMID and OSS. This decrease is more pronounced when we consider the hypothetical situation.
The reduction in the number of HIV deaths would be as a result of rolling out of ART as this increases the life expectancy of HIV positive individuals. Note that the proportion that are on ART with the two interventions are lower than the baseline proportion but only slightly and even though they are lower, the proportion of adult individuals ($[14, 50)$) tested for HIV increases with the interventions. This increase offsets some of the decrease in the ART proportions which results in a higher number of individuals on ART with the interventions than at baseline, and this leads to aversion of HIV deaths.

On the other hand, the number of TB deaths are changed negligibly by the interventions. In the hypothetical situation, the number of deaths just reduces by 1 which shows that even with 100% coverage of interventions and increase in the effect of the interventions, there is little effect on mortality of TB individuals.
The reason for this is that the proportion of TB patients that reports to the clinic, proportion which is tested and treated is small (all < 0.45). This is the major problem facing the TB management health system in Uganda [167, 168]. There are a number of delays such as patient delay (patients do not report to the health centres early), health system delays [170] and as such the baseline proportions of TB patients reporting, tested and treated are low. This is worsened by the fact that most of the clinics in our study were in rural areas. The implication for this is that even if coverage of training of MLPs in TB case management is increased, the mentioned barriers and problems need to be addressed if the training is to have considerable impact.

ART enrollment Results with the actual effects of IMID and OSS on the performance indicators show a decrease in the number of HIV positive individuals enrolled onto ART. This is because the interventions are purely training interventions with no other additives such as ascertaining availability of drug supplies. Though the interventions increase the number that are tested and those that get into HIV care, they can not do anything about getting them onto ART when there are no drugs available. This has been noted as one of the barriers of ART provision and ART coverage [94].
However, when we consider the hypothetical situation of a 25% effect on IMID and OSS, there are some improvements seen which shows that if there are drugs are available then more individuals will be able to get onto ART.

TB recoveries The actual results on the cumulative number of TB recovereds show that there is a decrease in this number with the interventions as compared to baseline. It is more with IMID than with IMID+OSS. This is because the the proportion that initiated treatment declined with IMID but increased with IMID+OSS as compared to baseline and the proportion of individuals that completed treatment decreased during the period of both interventions.
When coverage of the interventions is increased to 100% and the effects on the performance

indicators are increased by 25%, 2 more active TB individuals recover with reference to baseline. Though the number of TB recovered individuals is small, the result proposes that increasing the coverage of training interventions can have positive impacts on patient recovery. However, the gains in TB recoveries are still small and this poses the same concern about the barriers that are experienced by the TB case management system in Uganda that have been noted in other studies [167, 168, 170].

Study limitations One of the limitations that we had for this study were that there were no integrated data which calls for more advances in integrated health services. Although there have been some efforts with HIV-TB services [139, 153] and some work with malaria-pneumonia [54, 75, 98], a lot more needs to be done.

The other limitation was the limited literature on some coinfections such as TB-pneumonia, TB-malaria and coinfections with three or more diseases. This presented a huge problem when searching for parameter values.

6.7 Summary

In this Chapter, we have developed a model of four infectious diseases: HIV, TB, malaria and pneumonia (HTMP model). We have given an overview of the existing coinfections and have parametrised the model in accordance to being HIV positive or HIV negative.

We simulated the HTMP model for the effect of IMID, combination effect of IMID and OSS on the integrated management of the four diseases in terms of deaths, ART enrollment and TB recovery. The results have demonstrated that training of MLPs and maintaining or increasing the coverage of training has the potential to improve quality of health care and to yield gains in survival and reduce the morbidity of patients. However, they also highlight that training alone is not enough and other factors such as availability of drug supplies and equipment are necessary for a substantial effect.

Chapter 7

Conclusions and Recommendations

In this thesis, we have investigated the effect of two training interventions on infectious diseases by formulating and studying three mathematical models: one that describes malaria-pneumonia coinfection, a second that considers HIV-TB coinfection and lastly, one that incorporates all the four diseases together. A qualitative analysis of the non age structured sub models of malaria, pneumonia, HIV and TB was done and also the effects of the two training interventions, IMID and IMID+OSS, together with the incremental impact of OSS on malaria-pneumonia coinfection, HIV-TB coinfection were estimated. These results are presented in Chapters 4, 5 and 6 of this thesis.

An overview of the results in Chapter 4 is as follows:

(i) Mathematical analysis of the non age structured model of malaria showed that it had a DFE with $m = 0$. Depending on the value of the infection rate from human to vector and the death rate of the mosquito, the results proposed that there is existence of a unique endemic equilibrium that is locally asymptotically stable whenever $R_0^M > 1$ or possibility of the phenomenon of backward bifurcation in which the epidemiological requirement of disease eradication of $R_0^M < 1$ no longer holds.

(ii) The analysis of the non age structured model of pneumonia showed that it had a DFE with $p = 0$ and a unique endemic equilibrium that is locally asymptotically stable whenever $R_0^P > 1$. This means that pneumonia disease will persist in the population if the reproductive number is greater than unity and it will die out if it is less than

unity.

(iii) The mathematical analysis was performed for the small models of malaria and pneumonia with constant parameters and not for the models with time dependent parameters. The results of these models are limited in their implications on the models with time dependent parameters. Nevertheless, we did gain some useful insights from the analysis.

(iv) IMID and IMID with OSS lead to a reduction in the number of cases, deaths and no change in disease incidence for malaria and pneumonia.

(v) Triaging contributes a lot to the effect of training of MLPs. It contributes more than 50% to that effect in reduction of deaths and its contribution ranges from 14% to 63% in reduction of disease cases.

(vi) Overall, training of MLPs has a positive effect on patient outcomes such as morbidity and mortality but not on the incidence of disease episodes. This shows the usefulness of case management interventions and highlights the importance of prevention of transmission interventions.

Conclusions from Chapter 5 are given below:

(i) The qualitative analysis of the model of HIV only showed that it has an endemic equilibrium that is locally asymptotically stable. This implies that for parameters that give $R_0^H > 1$, we have disease persisting in the population.

(ii) The qualitative analysis of the model of TB showed that it had multiple endemic equilibria and exhibited backward bifurcation. The implication of this occurrence is that the classical epidemiological requirement for effective eradication of TB, R_0^T to be less than one, is no longer sufficient, even though necessary. In fact, for the disease to be eradicated, the reproductive number must be smaller than a critical value less than one.

(iii) The cumulative number of HIV positive babies at birth decreased, the cumulative number of HIV exposed babies that got HIV positive through breastfeeding increased during the period of the interventions of IMID and IMID+OSS. IMID and IMID+OSS

also decreased the cumulative number of TB recovered, the cumulative number going onto ART and decreased the cumulative number of deaths in individuals not onto ART for the period of the intervention.

(iv) For the additional five years, most of the effects of IMID and those of the combination intervention of IMID and OSS stayed the same except for the case of the cumulative number of deaths of HIV positive individuals not on ART which increased with the interventions as compared to baseline.

(v) Increase in proportion of individuals tested for HIV testing and TB testing plays a major role in getting patients into HIV care or TB care and even if the proportions that initiate TB treatment and ART decrease slightly, considerable reduction in HIV infections and increase in recovered TB individuals is seen.

(vi) The results highlighted the problem of the health system delays in management of TB patients and also the unavailability of drugs that delay ART initiation and CTX provision.

Conclusions from Chapter 6 are given below:

(i) Merging of all the four diseases into the HTMP model and running simulations for the cumulative number of deaths yielded similar results as those that were obtained in the Chapters 4 and 5.

(ii) The hypothetical situation of using 100% coverage of the interventions and a 25% effect on IMID and OSS indicators yielded more positive impact on patient outcomes of mortality and morbidity.

Conclusions overall

(i) Training of MLPs has the potential to improve quality of health care and improve patient outcomes such as mortality and morbidity. Moreover, for diseases such as malaria and pneumonia, training of MLPs is very effective because there is already a good baseline (performance indicator proportions are high) to start with.
However for TB and HIV where the baseline is not good (performance indicator

proportions are low), training is not enough and other problems such as patient and health system delays for TB patients, availability of drugs and equipment supplies need to be addressed.

7.1 Contribution

(i) This is the first time a model using non-linear ordinary differential equations has been formulated to explicitly study the effect of training interventions. The model was used to estimate the effect of two training interventions on infectious diseases of malaria, pneumonia, HIV and TB relating it to patient outcomes such as mortality and morbidity.
It has the advantage that it incorporates the transmission dynamics of the diseases. It also used most of the available information such as Spectrum software, Uganda HIV reports and WHO reports.

(ii) Modelling of malaria-pneumonia coinfection and modelling of four diseases together is novel. Numerical simulations using the malaria-pneumonia coinfection model showed that triaging contributes more than 50% to the effect of training of MLPs in the reduction of deaths. The malaria-pneumonia coinfection model showed that a life per month is saved for children under five years of age with the implementation of the training interventions. Furthermore, it was shown that there was no change in incidence of diseases even though there was a reduction in the number of cases.
Numerical simulations for the HTMP model suggested that increasing the coverage of the interventions and their effect, increased the number of patient recoveries even in the current state of lack of adequate drugs, supplies and equipment.

(iii) Incorporation of the effect of CTX in a mathematical model is also an addition to knowledge. The model displayed a reduction in the number of HIV positive deaths by CTX initially but since the coverage of CTX remained almost unchanged for the entire period of the intervention, the number of HIV positive deaths started to increase after some time.

(iv) Fitting the malaria and pneumonia model to data using an optimization tool built in Matlab and estimating certain parameters is also an added advantage of our work as

most of the mathematical models are simulated without using data.

7.2 Limitations and future research

These were the limitations that we faced in this study:

(i) Lack of data for validation of models is a limitation. In our study, we relied mostly on malaria data when modelling the malaria-pneumonia coinfection and there were no time series data for HIV and TB.

(ii) For HIV and TB, we used parameter values for certain groups of individuals such as the coinfected HIV-TB individuals to represent all the HIV positive individuals.

(iii) There was limited literature on coinfections of TB with pneumonia or malaria and also little literature on three or more coinfections and this presented a problem in our search for parameter values.

For future research, the following can be considered:

(i) Having separate classes for symptomatic and asymptomatic individuals.

(ii) Differentiating the effect of ART from that of PMTCT.

(iii) Modelling the effect of CTX explicitly.

Appendix A

Centre Manifold Theorem

Theorem A.0.1 *Consider the following general system of ordinary differential equations with a parameter, ϕ*

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R} \text{ and } f \in C^2(\mathbb{R}^n \times \mathbb{R}),$$

where 0 is an equilibrium point of the system (that is, $f(0, \phi) \equiv 0$ for all ϕ) and assume

A1: $A = D_x f(0, 0) = (\frac{\partial f_i}{\partial x_i}(0, 0))$ is the linearisation matrix of the system (3.1) around the equilibrium, 0 with ϕ evaluated at 0. Zero is a simple eigenvalue of A and other eigenvalues of A have negative real parts;

A2: Matrix A has a right eigenvector w and a left eigenvector v (each corresponding to the zero eigenvalue).

Let f_r be the r^{th} component of f and

$$a = \sum_{r,i,j=1}^{n} v_r w_i w_j \frac{\partial^2 f_r}{\partial x_i \partial x_j}(0, 0),$$

$$b = \sum_{r,i=1}^{n} v_r w_i \frac{\partial^2 f_r}{\partial x_i \partial \phi}(0, 0).$$

The local dynamics of the system around 0 is totally determined by the signs of a and b.

1. *$a > 0$, $b > 0$. When $\phi < 0$ with $|\phi| << 1$, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0 < \phi << 1$, 0 is unstable and there exists a negative, locally asymptotically stable equilibrium;*

2. *$a < 0$, $b < 0$. When $\phi < 0$ with $|\phi| << 1$, 0 is unstable; when $0 < \phi << 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;*

3. $a > 0,\ b < 0$. *When* $\phi < 0$ *with* $|\phi| << 1$, 0 *is unstable; and there exists a locally asymptotically stable equilibrium; when* $0 < \phi << 1$, 0 *is stable, and a positive unstable equilibrium appears;*

4. $a < 0,\ b > 0$. *When* ϕ *changes from negative to positive,* 0 *changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable.*

   Particularly, if $a > 0,\ b > 0$, *then a backward bifurcation occurs at* $\phi = 0$.

We apply Theorem A.0.1 to the system of equations of malaria, pneumonia, HIV and TB.

A.1 Malaria

The Jacobian of the shifted system of equations (4.1a)–(4.1e) at $\beta_{vh} = \beta^*_{vh}$ has the following eigenvalues,

$$\left\{ 0, -\mu, -\mu_v, -\tfrac{1}{2}\left(-K_{10} \pm \tfrac{1}{K}\sqrt{(K(-4KK_5^* - 4K_{11}\mu_v + KK_{10}^2)}\right) \right\},$$

where

$$\begin{aligned} K_{10} &= (\theta_M + r_M + \alpha_M + \mu_M + \mu_{\widetilde{M}} + \mu_v), \\ K_{11} &= \alpha_M^2 + (\theta_M + \mu_{\widetilde{M}})^2 + \alpha_M(2\theta_M + r_M + \mu_M + \mu_M^2), \end{aligned}$$

and K, K_5^* have been defined in equations (4.4a) and (4.6b) respectively.

We find the right and left eigenvectors associated with the zero eigenvalue. The right eigenvector, $w = [w_1, w_2, w_3, w_4, w_5]^T$ is given as:

$$w_1 = -\frac{B\mu_v^2 K_1}{\mu^2 b_v \beta_{hv} K},\ w_2 = \frac{B\mu_v^2(\theta_M + \mu_{\widetilde{M}})}{\mu b_v \beta_{hv} K},\ w_3 = \frac{B\alpha_M \mu_v^2}{\mu b_v \beta_{hv} K},\ w_4 = -1,\ w_5 = 1.$$

The left eigenvector, $v = [v_1, v_2, v_3, v_4, v_5]^T$ is given as:

$$v_1 = 0,\ v_2 = \frac{b_v \mu \beta_{hv} K}{B\mu_v K_5^*},\ v_3 = \frac{b_v \mu \beta_{hv}(\theta_M + r_M + \alpha_M + \mu_M)}{B\mu_v K_5^*},\ v_4 = 0,\ v_5 = 1.$$

where K, K_1 and K_5^* are defined in equations (4.4a) and (4.6b).

We then compute a and b. We look for the non-zero partial derivatives of f at DFE. Since $v_1 = 0$, $v_4 = 0$ then the partial derivatives of f_1 and f_4 will cancel out after substitution. For calculation of a, the partial derivatives of f_3 also vanish. The remaining non-vanishing partial derivatives of f_2 and f_5 are:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{m_1 \mu^2 b_{_v} \beta_{_{vh}}}{B^2 \mu_{_v}}.$$

$$\frac{\partial^2 f_2}{(\partial x_2)^2} = \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = \frac{\partial^2 f_2}{(\partial x_3)^2} = \frac{2 m_1 \mu^2 b_{_v} \beta_{_{vh}}}{B^2 \mu_{_v}}.$$

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_5} = \frac{\partial^2 f_2}{\partial x_5 \partial x_2} = \frac{\partial^2 f_2}{\partial x_5 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_5} = -\frac{m_1 \beta_{_{vh}} \mu}{B}.$$

$$\frac{\partial^2 f_5}{\partial x_2 \partial x_4} = \frac{\partial^2 f_5}{\partial x_3 \partial x_4} = \frac{\partial^2 f_5}{\partial x_4 \partial x_2} = \frac{\partial^2 f_5}{\partial x_4 \partial x_3} = \frac{\beta_{_{vh}} \mu}{B}.$$

For the computation of b, the non-zero partial derivatives are given by:

$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*_{_{vh}}} = \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*_{_{vh}}} = -\frac{m 1 \mu b_{_v}}{B \mu_{_v}}, \quad \frac{\partial^2 f_2}{\partial x_5 \partial \beta^*_{_{vh}}} = m_1.$$

A.2 Pneumonia

The Jacobian of the shifted system of equations (4.7a)–(4.7c) at $\beta_{_P} = \beta^*_{_P}$ has the following eigenvalues,

$$\left\{ 0, -\mu, -\frac{\alpha^2_{_P} + (\theta_{_P} + \mu_{_{\tilde{P}}})^2 + \alpha_{_P}(2\theta_{_P} + r_{_P} + \mu_{_P} + \mu_{_{\tilde{P}}})}{\theta_{_P} + \alpha_{_P} + \mu_{_{\tilde{P}}}} \right\}.$$

We find the right and left eigenvectors associated with the zero eigenvalue. The right eigenvector, $w = [w_1, w_2, w_3]^T$ is given as:

$$w_1 = -\frac{\theta_{_P} \mu_{_P} + \mu_{_{\tilde{P}}}(\alpha_{_P} + \mu_{_P})}{\mu \alpha_{_P}}, \quad w_2 = \frac{\theta_{_P} + \mu_{_{\tilde{P}}}}{\alpha_{_P}}, \quad w_3 = 1.$$

The left eigenvector, $v = [v_1, v_2, v_3]^T$ is given as:

$$v_1 = -\mu, \quad v_2 = v_3 = 0.$$

To calculate a and b, we look for the non-vanishing partial derivatives of f at DFE. Since $v_2 = 0$, $v_3 = 0$, then the partial derivatives of f_2 and f_3 will cancel out after substitution. For computation of a, the non-zero partial derivatives of f_1 are:

$$\frac{\partial^2 f_1}{(\partial x_2)^2} = \frac{\partial^2 f_1}{\partial x_2 \partial x_3} = \frac{\partial^2 f_1}{\partial x_3 \partial x_2} = \frac{\partial^2 f_1}{(\partial x_3)^2} = \frac{2p_1 \mu \beta_{_P}}{B}.$$

For the computation of b, the non-vanishing partial derivatives are given by:

$$\frac{\partial^2 f_1}{\partial x_2 \partial \beta^*_{_P}} = \frac{\partial^2 f_1}{\partial x_3 \partial \beta^*_{_P}} = -p1.$$

A.3 HIV

The Jacobian of shifted system of equations (5.2a)–(5.2c) at $\beta_{_H} = \beta^*_{_H}$ has the following eigenvalues,

$$\left\{ 0, -\mu, -\frac{f_H^2 + 2f_H r_H + r_H^2 + r_H \mu_{S_1} + 2f_H \mu_{S_2} + r_H \mu_{S_2} + \mu_{S_2}^2}{f_H + r_H + \mu_{S_2}} \right\}.$$

We find the right and left eigenvectors associated with the zero eigenvalue.
The right eigenvector, $w = [w_1, w_2, w_3]^T$ is given as:

$$\begin{aligned} w_1 &= -\frac{f_{_H}\mu_{S_1} + r_{_H}\mu_{S_2} + \mu_{S_1}\mu_{S_2}}{\mu r_{_H}}, \\ w_2 &= \frac{f_{_H} + \mu_{S_2}}{r_{_H}}, \\ w_3 &= 1. \end{aligned}$$

The left eigenvector, $v = [v_1, v_2, v_3]^T$ is given as:

$$\begin{aligned} v_1 &= 0, \\ v_2 &= \frac{f_{_H} + r_{_H} + \mu_{S_2}}{f_{_H} + r_{_H} + \mu_{S_1}}, \\ v_3 &= 1. \end{aligned}$$

To compute a and b, we find the non-zero partial derivatives of f at DFE. Since $v_1 = 0$, then the partial derivatives of f_1 will cancel out after substitution.
For calculation of a, we use the non-zero partial derivatives of f_1 and these are:

$$\frac{\partial^2 f_2}{\partial x_1 \partial x_2} = \frac{\beta_{_H}(B-\mu)}{B}, \quad \frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{\beta_{_H}(B-\mu)}{B}, \quad \frac{\partial^2 f_2}{\partial x_2 \partial x_1} = \frac{\beta_{_H}(B-\mu)}{B}, \quad \frac{\partial^2 f_2}{(\partial x_2)^2} = -\frac{2\beta_{_H}\mu}{B},$$

$$\frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{\beta_{_H}(B-\mu)}{B}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{\beta_{_H}(B-\mu)}{B}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = \frac{\beta_{_H}(B-\mu)}{B}, \quad \frac{\partial^2 f_2}{(\partial x_3)^2} = -\frac{2\beta_{_H}\mu}{B}.$$

For the computation of b, the non-zero partial derivatives are given by:

$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*_{_H}} = 1, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta^*_{_H}} = 1.$$

A.4 TB

The Jacobian of the shifted system of equations (5.4a)–(5.4b) at $\beta_{_T} = \beta^*_{_T}$ has the following eigenvalues:

$$\left\{ 0, -\mu \right\}.$$

We find the right and left eigenvectors associated with the zero eigenvalue. The right eigenvector, $w = [w_1, w_2]^T$ is given as:

$$\begin{aligned} w_1 &= \frac{-\mu_{_I}}{\mu}, \\ w_2 &= 1. \end{aligned}$$

The left eigenvector, $v = [v_1, v_2]^T$ is given as:

$$\begin{aligned} v_1 &= 1, \\ v_2 &= 0. \end{aligned}$$

We then compute a and b. We look for the non-zero partial derivatives of f at DFE. Since $v_2 = 0$, then the partial derivatives of f_2 will cancel out after substitution. The non-zero

partial derivatives of f_1 are:

$$\frac{\partial^2 f_1}{\partial x_2 \partial x_1} = -e_1\beta_{_T} + \frac{e_1\beta_{_T}\mu}{B}, \quad \frac{\partial^2 f_1}{(\partial x_2)^2} = \frac{2e_1\mu\beta_{_T}}{B}.$$

For the computation of b, we look for the non-zero partial derivatives of f at DFE. We neglect the partial derivatives of f_1 since $v_1 = 0$. Thus the non-zero partial derivatives are given by:

$$\frac{\partial^2 f_2}{\partial x_2 \partial \beta^*_{_T}} = \frac{e_1\mu}{B}.$$

Appendix B

HTMP Model Equations

In this section, we present the model equations for the age-structured model of HIV, TB, malaria and pneumonia.

$$\begin{aligned}
\frac{dS_c}{dt} &= B - b_f + r_{P_c}P_c + r_{M_c}M_c + zr_{PM_c}PM_c + r_{T_c}I_c - (\lambda_{T_c}e'_c + \nu e_c)S_c \\
&\quad -(\lambda_{P_c}p'_c + \omega p_c + \lambda_{vh_c}m'_c + \vartheta m_c + \mu_{S_c} + \eta_1)S_c, \qquad \text{(B.1a)}\\
\frac{dS_b}{dt} &= \eta_1 S_c + r_{P_b}P_b + r_{M_b}M_b + zr_{PM_b}PM_b + r_{T_b}I_b - (\lambda_{T_b}e'_b + \nu e_b)S_b \\
&\quad -(\lambda_{P_b}p'_b + \omega p_b + \lambda_{M_b}m'_b + \vartheta m_b + \mu_{S_b} + \eta_2)S_b \qquad \text{(B.1b)}\\
\frac{dS_a}{dt} &= \eta_2 S_b - \lambda_H S_a + r_{P_a}P_a + r_{M_a}M_a + zr_{PM_a}PM_a + r_{T_a}I_a - \lambda_{T_a}e'_a S_a \\
&\quad -(\nu e_a + \lambda_{P_a}p'_a + \omega p_a + \lambda_{M_a}m'_a + \vartheta m_a + \mu_{S_a} + \eta_3)S_a, \qquad \text{(B.1c)}\\
\frac{dP_c}{dt} &= (\lambda_{P_c}p'_c + \omega p_c)S_c + z_2 r_{M_c}PM_c + \theta_1 q_1 \widetilde{PM_c} - (\lambda_{vh_c}m'_c + \vartheta m_c)P_c \\
&\quad -(r_{P_c} + \alpha_{P_c} + \mu_{P_c} + \eta_1)P_c, \qquad \text{(B.1d)}\\
\frac{dP_j}{dt} &= \eta_i P_{j-1} + (\lambda_{P_j}p'_j + \omega p_j)S_j + z_2 r_{M_j}PM_j + \theta_1 q_1 \widetilde{PM_j} - \lambda_{vh_j}m'_j P_j \\
&\quad -(\vartheta m_j + r_{P_j} + \alpha_{P_j} + \mu_{P_j} + \eta_{i+1})P_j,\ j = b, a,\ i = 1, 2 \qquad \text{(B.1e)}\\
\frac{dM_c}{dt} &= (\lambda_{vh_c}m'_c + \vartheta m_c)S_c + z_1 r_{P_c}PM_c + \theta_2 q_2 \widetilde{PM_c} - (\lambda_{P_c}p'_c + \omega p_c)M_c \\
&\quad -(r_{M_c} + \alpha_{M_c} + \mu_{M_c} + \eta_1)M_c, \qquad \text{(B.1f)}\\
\frac{dM_j}{dt} &= \eta_i M_{j-1} + (\lambda_{vh_j}m'_j + \vartheta m_j)S_j + z_1 r_{P_j}PM_j + \theta_2 q_2 \widetilde{PM_j} - \lambda_{P_j}p'_j M_j \\
&\quad -(\omega p_j + r_{M_j} + \alpha_{M_j} + \mu_{M_j} + \eta_{i+1})M_j, \qquad \text{(B.1g)}\\
\frac{dPM_c}{dt} &= (\lambda_{vh_c}m'_c + \vartheta m_c)P_c + (\lambda_{P_c}p'_c + \omega p_c)M_c + \theta q \widetilde{PM_c} - zr_{PM_c}PM_c \\
&\quad -(z_1 r_{P_c} + z_2 r_{M_c} + \alpha_{PM_c} + \mu_{PM_c} + \eta_1)PM_c, \qquad \text{(B.1h)}\\
\frac{dPM_j}{dt} &= \eta_i PM_{j-1} + (\lambda_{vh_j}m'_j + \vartheta m_j)P_j + (\lambda_{P_j}p'_j + \omega p_j)M_j + \theta q \widetilde{PM_j} \\
&\quad -(zr_{PM_j} + z_1 r_{P_j} + z_2 r_{M_j} + \alpha_{PM_j} + \mu_{PM_j} + \eta_{i+1})PM_j, \qquad \text{(B.1i)}\\
\frac{d\widetilde{PM_c}}{dt} &= \alpha_{P_c}P_c + \alpha_{M_c}M_c + \alpha_{PM_c}PM_c - (\theta + \mu_{\widetilde{PM_c}} + \eta_1)\widetilde{PM_c}. \qquad \text{(B.1j)}\\
\frac{d\widetilde{PM_j}}{dt} &= \eta_i PM_{j-1} + \alpha_{P_j}P_j + \alpha_{M_j}M_j + \alpha_{PM_j}PM_j - (\theta + \mu_{\widetilde{PM_j}} + \eta_{j+1})\widetilde{PM_j}. \qquad \text{(B.1k)}
\end{aligned}$$

$$\frac{dI_c}{dt} = (\lambda_{T_c} e'_c + \nu e_c)S_c + r_{P_c} IP_c + r_{M_c} IM_c + zr_{PM_c} IPM_c - r_{T_c} I_c \quad \text{(B.2a)}$$
$$-(\lambda_{P_c} p'_c + \omega p_c + \lambda_{vh_c} m'_c + \vartheta m_c + \mu_{I_c} + \eta_1)I_c,$$

$$\frac{dI_b}{dt} = \eta_1 I_c + (\lambda_{T_b} e'_b + \nu e_b)S_b + r_{P_b} IP_b + r_{M_b} IM_b + zr_{PM_b} IPM_b - r_{T_b} I_b \quad \text{(B.2b)}$$
$$-(\lambda_{P_b} p'_b + \omega p_b + \lambda_{M_b} m'_b + \vartheta m_b + \mu_{I_b} + \eta_2)I_b,$$

$$\frac{dI_a}{dt} = \eta_2 I_b + (\lambda_{T_a} e'_a + \nu e_a)S_a + r_{P_a} IP_a + r_{M_a} IM_a + zr_{PM_a} IPM_a - r_{T_a} I_a \quad \text{(B.2c)}$$
$$-(\lambda_H + \lambda_{P_a} p'_a + \omega p_a + \lambda_{M_a} m'_a + \vartheta m_a + \mu_{I_a} + \eta_3)I_a,$$

$$\frac{dIP_c}{dt} = (\lambda_{P_c} p'_c + \omega p_c)I_c + z_2 r_{M_c} IPM_c + \theta_1 q_1 \widetilde{IPM}_c - (r_{P_c} + \lambda_{vh_c} m'_c)IP_c \quad \text{(B.2d)}$$
$$-(\vartheta m_c + \alpha_{IP_c} + \mu_{IP_c} + \eta_1)IP_c,$$

$$\frac{dIP_j}{dt} = \eta_i IP_{j-1} + (\lambda_{P_j} p'_j + \omega p_j)I_j + z_2 r_{M_j} IPM_j + \theta_1 q_1 \widetilde{IPM}_j - r_{P_j} IP_j \quad \text{(B.2e)}$$
$$-(\lambda_{vh_j} m'_j + \vartheta m_j + \alpha_{IP_j} + \mu_{IP_j} + \eta_{i+1})IP_j,$$

$$\frac{dIM_c}{dt} = (\lambda_{vh_c} m'_c + \vartheta m_c)I_c + z_1 r_{P_c} IPM_c + \theta_2 q_2 \widetilde{IPM}_c - (r_{M_c} + \lambda_{P_c} p'_c)IM_c \quad \text{(B.2f)}$$
$$-(\omega p_c + \alpha_{IM_c} + \mu_{IM_c} + \eta_1)IM_c,$$

$$\frac{dIM_j}{dt} = \eta_i IM_{j-1} + (\lambda_{vh_j} m'_j + \vartheta m_j)I_j + z_1 r_{P_j} IPM_j + \theta_2 q_2 \widetilde{IPM}_j - r_{M_j} IM_c \quad \text{(B.2g)}$$
$$-(\lambda_{P_j} p'_j + \omega p_j + \alpha_{IM_j} + \mu_{IM_j} + \eta_{i+1})IM_j,$$

$$\frac{dIPM_c}{dt} = (\lambda_{vh_c} m'_c + \vartheta m_c)IP_c + (\lambda_{P_c} p'_c + \omega p_c)IM_c + \theta q \widetilde{IPM}_c - zr_{PM_c} IPM_c \quad \text{(B.2h)}$$
$$-(z_2 r_{M_c} + z_1 r_{P_c} + \alpha_{IPM_c} + \mu_{IPM_c} + \eta_1)IPM_c,$$

$$\frac{dIPM_j}{dt} = \eta_i IPM_{j-1} + (\lambda_{vh_j} m'_j + \vartheta m_j)IP_j + (\lambda_{P_j} p'_j + \omega p_j)IM_j + \theta q \widetilde{IPM}_j \quad \text{(B.2i)}$$
$$-(zr_{PM_j} IPM_j + z_2 r_{M_j} + z_1 r_{P_j} + \alpha_{IPM_j} + \mu_{IPM_j} + \eta_{i+1})IPM_j,$$

$$\frac{d\widetilde{IPM}_c}{dt} = \alpha_{IP_c} IP_c + \alpha_{IM_c} IM_c + \alpha_{IPM_c} IPM_c - (\theta + \mu_{\widetilde{IPM}_c} + \eta_1)\widetilde{IPM}_c, \quad \text{(B.2j)}$$

$$\frac{d\widetilde{IPM}_j}{dt} = \eta_i IPM_{j-1} + \alpha_{IP_j} IP_j + \alpha_{IM_j} IM_j + \alpha_{IPM_j} IPM_j - \theta \widetilde{IPM}_j \quad \text{(B.2k)}$$
$$-(\mu_{\widetilde{IPM}_j} + \eta_{i+1})\widetilde{IPM}_j.$$

$$\begin{aligned}
\frac{dS1_c}{dt} &= B_1 + b_f + f_{H_c} S2_c + r_{P_c^1} S1P_c + r_{M_c^1} S1M_c + zr_{PM_c} S1PM_c + r_{T_c} I1_c \quad \text{(B.3a)}\\
&\quad -(\lambda_{P_c} p'_{1c} + \omega_1 p_c) S1_c - (\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c + \lambda_{T_c} e'_{1c} + \nu_1 e_c) S1_c\\
&\quad -(r_{H_c} + (\mu_0(1-\gamma p_s) + \mu_1 \gamma p_s) + \eta_1) S1_c,\\
\frac{dS1_b}{dt} &= \eta_1 S1_c + f_{H_b} S2_b + r_{P_b^1} S1P_b + r_{M_b^1} S1M_b + zr_{PM_b} S1PM_b + r_{T_b} I1_b \quad \text{(B.3b)}\\
&\quad -(\lambda_{P_b} p'_{1b} + \omega_1 p_b) S1_b - (\lambda_{M_b} m'_{1b} + \vartheta_1 m_b + \lambda_{T_b} e'_{1b} + \nu_1 e_b) S1_b\\
&\quad -(r_{H_b} + (\mu_0(1-\gamma p_s) + \mu_1 \gamma p_s) + \eta_2) S1_b,\\
\frac{dS1_a}{dt} &= \eta_2 S1_b + \lambda_H S_a + f_{H_a} S2_a + r_{P_a^1} S1P_a + r_{M_a^1} S1M_a + zr_{PM_a} S1PM_a \quad \text{(B.3c)}\\
&\quad +r_{T_a} I1_a - (\lambda_{P_a} p'_{1a} + \omega_1 p_a) S1_a - (\lambda_{M_a} m'_{1a} + \vartheta_1 m_a + \lambda_{T_a} e'_{1a}) S1_a\\
&\quad -(\nu_1 e_a + r_{H_a} + (\mu_0(1-\gamma p_s) + \mu_1 \gamma p_s) + \eta_3) S1_a,\\
\frac{dS1P_c}{dt} &= (\lambda_{P_c} p'_{1c} + \omega_1 p_c) S1_c + z_2 r_{M_c^1} S1PM_c + \theta_1 q_1 \widetilde{S1PM}_c - r_{P_c^1} S1P_c \quad \text{(B.3d)}\\
&\quad -(\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c + \alpha_{S_1P_c} + \mu_{S_1P_c} + \eta_1) S1P_c,\\
\frac{dS1P_j}{dt} &= \eta_i S1P_{j-1} + (\lambda_{P_j} p'_{1j} + \omega_1 p_j) S1_j + z_2 r_{M_j^1} S1PM_j + \theta_1 q_1 \widetilde{S1PM}_j \quad \text{(B.3e)}\\
&\quad -(r_{P_j^1} + \lambda_{vh_j} m'_{1j} + \vartheta_1 m_j + \alpha_{S_1P_j} + \mu_{S_1P_j} + \eta_{i+1}) S1P_j,\\
\frac{dS1M_c}{dt} &= (\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c) S1_c + z_1 r_{P_c^1} S1PM_c + \theta_2 q_2 \widetilde{S1PM}_c - r_{M_c^1} S1M_c \quad \text{(B.3f)}\\
&\quad -(\lambda_{P_c} p'_{1c} + \omega_1 p_c + \alpha_{S_1M_c} + \mu_{S_1M_c} + \eta_1) S1M_c,\\
\frac{dS1M_j}{dt} &= \eta_i S1M_{j-1} + (\lambda_{vh_j} m'_{1j} + \vartheta_1 m_j) S1_j + z_1 r_{P_j^1} S1PM_j + \theta_2 q_2 \widetilde{S1PM}_j \quad \text{(B.3g)}\\
&\quad -(r_{M_j^1} + \lambda_{P_j} p'_{1j} + \omega_1 p_j + \alpha_{S_1M_j} + \mu_{S_1M_j} + \eta_{i+1}) S1M_j,\\
\frac{dS1PM_c}{dt} &= (\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c) S1P_c + (\lambda_{P_c} p'_{1c} + \omega_1 p_c) S1M_c + \theta q \widetilde{S1PM}_c \quad \text{(B.3h)}\\
&\quad -(zr_{PM_c} + z_1 r_{P_c^1} + z_2 r_{M_c^1} + \alpha_{S_1PM_c} + \mu_{S_1PM_c} + \eta_1) S1PM_c,\\
\frac{dS1PM_j}{dt} &= \eta_i S1PM_{j-1} + (\lambda_{vh_j} m'_{1j} + \vartheta_1 m_j) S1P_j + (\lambda_{P_j} p'_{1j} + \omega_1 p_j) S1M_j \quad \text{(B.3i)}\\
&\quad +\theta q \widetilde{S1PM}_j - (zr_{PM_j} + z_1 r_{P_j^1} + z_2 r_{M_j^1} + \alpha_{S_1PM_j} + \mu_{S_1PM_j}) S1PM_j\\
&\quad -\eta_{i+1} S1PM_j,\\
\frac{d\widetilde{S1PM}_c}{dt} &= \alpha_{S_1P_c} S1P_c + \alpha_{S_1M_c} S1M_c + \alpha_{S_1PM_c} S1PM_c - (\theta + \mu_{\widetilde{S1PM}_c}) \widetilde{S1PM}_c \quad \text{(B.3j)}\\
&\quad -\eta_1 \widetilde{S1PM}_c,\\
\frac{d\widetilde{S1PM}_j}{dt} &= \eta_i S1PM_{j-1} + \alpha_{S_1P_j} S1P_j + \alpha_{S_1M_j} S1M_j + \alpha_{S_1PM_j} S1PM_j \quad \text{(B.3k)}\\
&\quad -(\theta + \mu_{\widetilde{S1PM}_j} + \eta_{i+1}) \widetilde{S1PM}_j.
\end{aligned}$$

$$\begin{aligned}
\frac{dI1_c}{dt} &= (\lambda_{T_c} e'_{1c} + \nu_1 e_c) S1_c + f_{H^2_c} I2_c + r_{P^1_c} I_1 P_c + r_{M^1_c} I_1 M_c + z r_{PM_c} I_1 PM_c \qquad \text{(B.4a)}\\
&\quad -(\lambda_{P_c} p'_{1c} + \omega_1 p_c + \lambda_{vh_c} m'_{1c} + \vartheta_1 m_c) I1_c - (r_{H_c} + \mu_{I_{1_{c0}}}(1-\gamma p_s)) I1_c\\
&\quad -(\mu_{I_{1_{c1}}} \gamma p_s + r_{T^1_c} + \eta_1) I1_c,\\
\frac{dI1_b}{dt} &= \eta_1 I1_c + (\lambda_{T_b} e'_{1b} + \nu_1 e_b) S1_b + f_{H^2_b} I2_b + r_{P^1_b} I_1 P_b + r_{M^1_b} I_1 M_b \qquad \text{(B.4b)}\\
&\quad +z r_{PM_b} I_1 PM_b - (\lambda_{P_b} p'_{1b} + \omega_1 p_b + \lambda_{M_b} m'_{1b} + \vartheta_1 m_b) I1_b - r_{H_b} I1_b\\
&\quad -(\mu_{I_{1_{b0}}}(1-\gamma p_s) + \mu_{I_{1_{b1}}} \gamma p_s + r_{T^1_b} + \eta_1) I1_b,\\
\frac{dI1_a}{dt} &= \eta_2 I1_b + \lambda_H I_a + (\lambda_{T_a} e'_{1a} + \nu_1 e_a) S1_a + f_{H^2_a} I2_a + r_{P^1_a} I_1 P_a + r_{M^1_a} I_1 M_a \qquad \text{(B.4c)}\\
&\quad +z r_{PM_a} I_1 PM_a - (\lambda_{P_a} p'_{1a} + \omega_1 p_a + \lambda_{M_a} m'_{1a} + \vartheta_1 m_a) I1_a - r_{H_a} I1_a\\
&\quad -(\mu_{I_{1_{a0}}}(1-\gamma p_s) + \mu_{I_{1_{a1}}} \gamma p_s + r_{T^1_a} + \eta_1) I1_a,\\
\frac{dI_1P_c}{dt} &= (\lambda_{P_c} p'_{1c} + \omega_1 p_c) I1_c + r_{M^1_c} I_1 PM_c + \theta_1 q_1 \widetilde{I_1 PM}_c - r_{P^1_c} I_1 P_c \qquad \text{(B.4d)}\\
&\quad -(\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c + \alpha_{I_1 P_c} + \mu_{I_1 P_c} + \eta_1) I_1 P_c,\\
\frac{dI_1P_j}{dt} &= \eta_i I_1 P_{j-1} + (\lambda_{P_j} p'_{1j} + \omega_1 p_j) I1_j + z_2 r_{M^1_j} I_1 PM_j + \theta_1 q_1 \widetilde{I_1 PM}_j \qquad \text{(B.4e)}\\
&\quad -(r_{P^1_j} + \lambda_{vh_j} m'_{1j} + \vartheta_1 m_j + \alpha_{I_1 P_j} + \mu_{I_1 P_j} + \eta_{i+1}) I_1 P_j,\\
\frac{dI_1M_c}{dt} &= (\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c) I1_c + r_{P^1_c} I_1 PM_c + \theta_2 q_2 \widetilde{I_1 PM}_c - r_{M^1_c} I_1 M_c \qquad \text{(B.4f)}\\
&\quad -(\lambda_{P_c} p'_{1c} + \omega_1 p_c + \alpha_{I_1 M_c} + \mu_{I_1 M_c} + \eta_1) I_1 M_c,\\
\frac{dI_1M_j}{dt} &= \eta_i I_1 M_{j-1} + (\lambda_{vh_j} m'_{1j} + \vartheta_1 m_j) I1_j + z_1 r_{P^1_j} I_1 PM_j + \theta_2 q_2 \widetilde{I_1 PM}_j \qquad \text{(B.4g)}\\
&\quad -(r_{M^1_j} + \lambda_{P_j} p'_{1j} + \omega_1 p_j + \alpha_{I_1 M_j} + \mu_{I_1 M_j} + \eta_{i+1}) I_1 M_j,\\
\frac{dI_1PM_c}{dt} &= (\lambda_{vh_c} m'_{1c} + \vartheta_1 m_c) I_1 P_c + (\lambda_{P_c} p'_{1c} + \omega_1 p_c) I_1 M_c + \theta q \widetilde{I_1 PM}_c \qquad \text{(B.4h)}\\
&\quad -(z r_{PM_c} + z_1 r_{P^1_c} + z_2 r_{M^1_c} + \alpha_{I_1 PM_c} + \mu_{I_1 PM_c} + \eta_1) I_1 PM_c,\\
\frac{dI_1PM_j}{dt} &= \eta_i I_1 PM_j + (\lambda_{vh_j} m'_{1j} + \vartheta_1 m_j) I_1 P_j + (\lambda_{P_j} p'_{1j} + \omega_1 p_j) I_1 M_j \qquad \text{(B.4i)}\\
&\quad +\theta q \widetilde{I_1 PM}_j - (z r_{PM_j} + z_1 r_{P^1_j} + z_2 r_{M^1_j} + \alpha_{I_1 PM_j} + \mu_{I_1 PM_j} I_1 PM_j\\
&\quad -\eta_{i+1} I_1 PM_j,\\
\frac{d\widetilde{I_1 PM}_c}{dt} &= \alpha_{I_1 P_c} I_1 P_c + \alpha_{I_1 M_c} I_1 M_c + \alpha_{I_1 PM_c} I_1 PM_c - (\theta + \mu_{\widetilde{I_1 PM}_c}) \widetilde{I_1 PM}_c \qquad \text{(B.4j)}\\
&\quad -\eta_1 \widetilde{I_1 PM}_c,\\
\frac{d\widetilde{I_1 PM}_j}{dt} &= \eta_i \widetilde{I_1 PM}_{j-1} + \alpha_{I_1 P_c} I_1 P_c + \alpha_{I_1 M_c} I_1 M_c + \alpha_{I_1 PM_c} I_1 PM_c - \theta \widetilde{I_1 PM}_c \qquad \text{(B.4k)}\\
&\quad -(\mu_{\widetilde{I_1 PM}_c} + \eta_{i+1}) \widetilde{I_1 PM}_c.
\end{aligned}$$

$$\frac{dS_{2_c}}{dt} = r_{H_c}S_{1_c} + r_{P_c^2}S_2P_c + r_{M_c^2}S_2M_c + zr_{PM_c}S_2PM_c + r_{T_c}I_{2_c} - f_{H_c}S_{2_c} \quad \text{(B.5a)}$$
$$-(\lambda_{P_c}p'_{2c} + \omega_2 p_c + \lambda_{vh_c}m'_{2c} + \vartheta_2 m_c + \lambda_{T_c}e'_{2c} + \nu_2 e_c + \mu_{S_{2_c}})S_{2_c}$$
$$-\eta_1 S_{2_c},$$

$$\frac{dS_{2_j}}{dt} = \eta_i S_{2_{j-1}} + r_{H_j}S_{1_j} + r_{P_j^2}S_2P_j + r_{M_j^2}S_2M_j + zr_{PM_j}S_2PM_j + r_{T_j}I_{2_j} \quad \text{(B.5b)}$$
$$-(f_{H_j} + \lambda_{P_j}p'_{2j} + \omega_2 p_j + \lambda_{vh_j}m'_{2j} + \vartheta_2 m_j + \lambda_{T_j}e'_{2j} + \nu_2 e_j)S_{2_j}$$
$$-(\mu_{S_{2_j}} + \eta_{i+1})S_{2_j},$$

$$\frac{dS_2P_c}{dt} = (\lambda_{P_c}p'_{2c} + \omega_2 p_c)S_{2_c} + z_2 r_{M_c^2}S_2PM_c + \theta_1 q_1 \widetilde{S_2PM}_c - r_{P_c^2}S_2P_c \quad \text{(B.5c)}$$
$$-(\lambda_{vh_c}m'_{2c} + \vartheta_2 m_c + \alpha_{S_2P_c} + \mu_{S_2P_c} + \eta_1)S_2P_c,$$

$$\frac{dS_2P_j}{dt} = \eta_i S_2P_{j-1} + (\lambda_{P_j}p'_{2j} + \omega_2 p_j)S_{2_j} + z_2 r_{M_j^2}S_2PM_j + \theta_1 q_1 \widetilde{S_2PM}_j \quad \text{(B.5d)}$$
$$-(r_{P_j^2} + \lambda_{vh_j}m'_{2j} + \vartheta_2 m_j + \alpha_{S_2P_j} + \mu_{S_2P_j} + \eta_{i+1})S_2P_j,$$

$$\frac{dS_2M_c}{dt} = (\lambda_{vh_c}m'_{2c} + \vartheta_2 m_c)S_{2_c} + z_1 r_{P_c^2}S_2PM_c + \theta_2 q_2 \widetilde{S_2M}_c - r_{M_c^2}S_2M_c \quad \text{(B.5e)}$$
$$-(\lambda_{P_c}p'_{2c} + \omega_2 p_c + \alpha_{S_2M_c} + \mu_{S_2M_c} + \eta_1)S_2M_c,$$

$$\frac{dS_2M_j}{dt} = \eta_i S_2M_{j-1} + (\lambda_{vh_j}m'_{2j} + \vartheta_2 m_j)S_{2_j} + z_1 r_{P_j^2}S_2PM_j + \theta_2 q_2 \widetilde{S_2M}_j \quad \text{(B.5f)}$$
$$-(r_{M_j^2} + \lambda_{P_j}p'_{2j} + \omega_2 p_j + \alpha_{S_2M_j} + \mu_{S_2M_j} + \eta_{i+1})S_2M_j,$$

$$\frac{dS_2PM_c}{dt} = (\lambda_{vh_c}m'_{2c} + \vartheta_2 m_c)S_2P_c + (\lambda_{P_c}p'_{2c} + \omega_2 p_c)S_2M_c + \theta q \widetilde{S_2PM}_c \quad \text{(B.5g)}$$
$$-(zr_{PM_c} + z_1 r_{M_c^2} + z_2 r_{P_c^2} + \alpha_{S_2PM_c} + \mu_{S_2PM_c} + \eta_1)S_2PM_c,$$

$$\frac{dS_2PM_j}{dt} = \eta_i S_2PM_{j-1} + (\lambda_{vh_j}m'_{2j} + \vartheta_2 m_j)S_2P_j + (\lambda_{P_j}p'_{2j} + \omega_2 p_j)S_2M_j \quad \text{(B.5h)}$$
$$+\theta q \widetilde{S_2PM}_j - (zr_{PM_j} + z_1 r_{M_j^2} + z_2 r_{P_j^2} + \alpha_{S_2PM_j} + \mu_{S_2PM_j})S_2PM_j$$
$$-\eta_1 S_2PM_j,$$

$$\frac{d\widetilde{S_2PM}_c}{dt} = \alpha_{S_2P_c}S_2P_c + \alpha_{S_2M_c}S_2M_c + \alpha_{S_2PM_c}S_2PM_c - (\theta + \mu_{\widetilde{S_2PM}_c})\widetilde{S_2PM}_c \quad \text{(B.5i)}$$
$$-\eta_1 \widetilde{S_2PM}_c.$$

$$\frac{d\widetilde{S_2PM}_j}{dt} = \eta_i S_2PM_{j-1} + \alpha_{S_2P_j}S_2P_j + \alpha_{S_2M_j}S_2M_j + \alpha_{S_2PM_j}S_2PM_j \quad \text{(B.5j)}$$
$$-(\theta + \mu_{\widetilde{S_2PM}_j} + \eta_{i+1})\widetilde{S_2PM}_j.$$

$$\frac{dI2_c}{dt} = (\lambda_{T_c} e'_{2c} + \nu_2 e_c) S_{2_c} + r_{H_c^2} I1_c + r_{P_c^2} I2P_c + r_{M_c^2} I2M_c + z r_{PM_c} I2PM_c - (r_{T_c^2} + f_{H_c^2} + \lambda_{P_c} p'_{2c} + \omega_2 p_c + \lambda_{vh_c} m'_{2c} + \vartheta_2 m_c + \mu_{I2_c}) I2_c - \eta_1 I2_c, \tag{B.6a}$$

$$\frac{dI2_j}{dt} = \eta_i I2_{j-1} + (\lambda_{T_j} e'_{2j} + \nu_2 e_j) S_{2_j} + r_{H_j^2} I1_j + r_{P_j^2} I2P_j + r_{M_j^2} I2M_j + z r_{PM_j} I2PM_j - (r_{T_j^2} + f_{H_j^2} + \lambda_{P_j} p'_{2j} + \omega_2 p_j + \lambda_{vh_j} m'_{2j} + \vartheta_2 m_j) I2_j - (\mu_{I2_j} + \eta_{i+1}) I2_j, \tag{B.6b}$$

$$\frac{dI2P_c}{dt} = (\lambda_{P_c} p'_{2c} + \omega_2 p_c) I2_c + z_2 r_{M_c^2} I2PM_c + \theta q_1 \widetilde{I2PM}_c - r_{P_c^2} I2P_c - (\lambda_{vh_c} m'_{2c} + \vartheta_2 m_c + \alpha_{I_2P_c} + \mu_{I_2P_c} + \eta_1) I2P_c, \tag{B.6c}$$

$$\frac{dI2P_j}{dt} = \eta_i I2P_{j-1} + (\lambda_{P_j} p'_{2j} + \omega_2 p_j) I2_j + z_2 r_{M_j^2} I2PM_j + \theta q_1 \widetilde{I2PM}_j - (r_{P_j^2} + \lambda_{vh_j} m'_{2j} + \vartheta_2 m_j + \alpha_{I_2P_j} + \mu_{I_2P_j} + \eta_{i+1}) I2P_j, \tag{B.6d}$$

$$\frac{dI2M_c}{dt} = (\lambda_{vh_c} m'_{2c} + \vartheta_2 m_c) I2_c + z_1 r_{P_c^2} I2PM_c + \theta_2 q_2 \widetilde{I2PM}_c - r_{M_c^2} I2M_c - (\lambda_{P_c} p'_{2c} + \omega_2 p_c + \alpha_{I_2M_c} + \mu_{I_2M_c} + \eta_1) I2M_c, \tag{B.6e}$$

$$\frac{dI2M_j}{dt} = \eta_i I2M_{j-1} + (\lambda_{vh_j} m'_{2j} + \vartheta_2 m_j) I2_j + z_1 r_{P_j^2} I2PM_j + \theta_2 q_2 \widetilde{I2PM}_j - (r_{M_j^2} + \lambda_{P_j} p'_{2j} + \omega_2 p_j + \alpha_{I_2M_j} + \mu_{I_2M_j} + \eta_{i+1}) I2M_j, \tag{B.6f}$$

$$\frac{dI2PM_c}{dt} = (\lambda_{vh_c} m'_{2c} + \vartheta_2 m_c) I2P_c + (\lambda_{P_c} p'_{2c} + \omega_2 p_c) I2M_c + \theta q \widetilde{I2PM}_c - (z r_{PM_c} + z_1 r_{P_c^2} + z_2 r_{M_c^2} + \alpha_{I_2PM_c} + \mu_{I_2PM_c} + \eta_1) I2PM_c, \tag{B.6g}$$

$$\frac{dI2PM_j}{dt} = \eta_i I2PM_{j-1} + (\lambda_{vh_j} m'_{2j} + \vartheta_2 m_j) I2P_j + (\lambda_{P_j} p'_{2j} + \omega_2 p_j) I2M_j + \theta q \widetilde{I2PM}_j - (z r_{PM_j} + z_1 r_{P_j^2} + z_2 r_{M_j^2} + \alpha_{I_2PM_j} + \mu_{I_2PM_j}) I2PM_j - \eta_{i+1} I2PM_j, \tag{B.6h}$$

$$\frac{d\widetilde{I2PM}_c}{dt} = \alpha_{I_2P_c} I2P_c + \alpha_{I_2M_c} I2M_c + \alpha_{I_2PM_c} I2PM_c - (\theta + \mu_{\widetilde{I2PM}_c}) \widetilde{I2PM}_c - \eta_1 \widetilde{I2PM}_c, \tag{B.6i}$$

$$\frac{d\widetilde{I2PM}_j}{dt} = \eta_i \widetilde{I2PM}_{j-1} + \alpha_{I_2P_j} I2P_j + \alpha_{I_2M_j} I2M_j + \alpha_{I_2PM_j} I2PM_j - \theta \widetilde{I2PM}_j - (\mu_{\widetilde{I2PM}_j} + \eta_{i+1}) \widetilde{I2PM}_j. \tag{B.6j}$$

The mosquito dynamics are given by

$$\frac{dS_v}{dt} = b_v - (\lambda_{hv_c} + \lambda_{hv_b} + \lambda_{hv_a})S_v - \mu_v S_v, \tag{B.7a}$$

$$\frac{dI_v}{dt} = (\lambda_{hv_c} + \lambda_{hv_b} + \lambda_{hv_a})S_v - \mu_v I_v. \tag{B.7b}$$

With the system of equations (B.1a)–(B.1k), (B.2a)–(B.2k), (B.3a)–(B.3k), (B.4a)–(B.4k), (B.5a)–(B.5j),(B.6a)–(B.6j) and (B.7a)–(B.7b), we have the following definitions:

$$\begin{aligned}
p'_{1j} &= (\gamma p_s p_{1j} + (1-\gamma p_s)p_{0j}), \quad p_{1j} = pp^1_{2j} + (1-p)p^1_{1j}, \quad p_{0j} = pp^0_{2j} + (1-p)p^0_{1j}.\\
m'_{1j} &= (\gamma p_s m_{1j} + (1-\gamma p_s)m_{0j}), \quad m_{1j} = mm^1_{2j} + (1-m)m^1_{1j}, \quad m_{0j} = mm^0_{2j} + (1-m)m^0_{1j}.\\
e'_{1j} &= (\gamma p_s e'_{1j} + (1-\gamma p_s)e'_{0j}), \quad e_{1j} = ee^1_{2j} + (1-e)e^1_{1j}, \quad e_{0j} = ee^0_{2j} + (1-e)e^0_{1j}.
\end{aligned}$$

where $j = c, b, a$ stands for the age groups $[0, 5)$, $[5, 14)$ and $[14, 50)$ respectively. 0 represents not being on CTX and 1 represents being on CTX for the respective latent and symptomatic classes. The other definitions are:

i p^0_{1j}, m^0_{1j}, e^0_{1j} are the proportions of new infections of pneumonia, malaria and TB respectively that become symptomatic for HIV infected individuals not on CTX.

ii p^1_{1j}, m^1_{1j}, e^1_{1j} are the proportions of new infections of pneumonia, malaria and TB in turn that become symptomatic for HIV infected individuals on CTX.

iii p^0_{2j}, m^0_{2j}, e^0_{2j} are the proportions of reinfections of pneumonia, malaria and TB accordingly that become symptomatic for HIV infected individuals not on CTX.

iv p^1_{2j}, m^1_{2j}, e^1_{2j} are the proportions of reinfections of pneumonia, malaria and TB respective that become symptomatic for HIV infected individuals on CTX.

v $\lambda_{H_j} = \beta_{H_j} I_H/N$. β_{H_j} is the infection rate for HIV. I_H is the HIV infected human population and N is the total human population. Note that $\beta_{H_c} = \beta_{H_b} = 0$ thus $\lambda_{H_c} = \lambda_{H_b} = 0$.

vi $\lambda_{T_j} = (\beta_{T_j} I_T + \beta_{TH_j} I_{TH})/N$. β_{T_j} is the rate at which HIV negative active TB individuals pass on infection for the respective age groups and β_{TH_j} at which coinfected HIV-TB individuals transmit the TB infection.

vii $\lambda_{vh_j} = \beta_{vh_j} I_v/N$. β_{vh_j} is the rate at which a vector (mosquito) infects a human, I_v is the infected vector (mosquito) population and N is the human population.

viii $\lambda_{hv_j} = \beta_{hv_j}(I_M/N)$. β_{hv_j} is the rate at which a vector (mosquito) becomes infected by biting an infected human and I_M is the human population infected with malaria.

ix $\lambda_{P_j} = \beta_{P_j} I_P/N$. β_{P_j} is the rate at which individuals acquire pneumonia infection and I_P is the infected pneumonia population.

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